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RESPIRATORY CARE

A MONTHLY SCIENCE JOURNAL
45TH YEAR—ESTABLISHED 1956

SPECIAL ISSUE

CONSENSUS CONFERENCE ON AEROSOLS AND DELIVERY DEVICES

- Consensus Statement on Aerosols and Delivery Devices
- Influence of Inspiratory Flow Rate, Particle Size, and Airway Caliber on Aerosolized Drug Delivery to the Lung
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- A Clinician's Perspective on Aerosol Therapy

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NDC Number	Description	Concentration (mg/mL)	mL/Vial	Units Per Carton
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INDICATION AND USAGE
CUROSURF is indicated for the treatment (rescue) of Respiratory Distress Syndrome (RDS) in premature infants. CUROSURF reduces mortality and pneumothoraces associated with RDS.

CLINICAL STUDIES
The clinical efficacy of CUROSURF was demonstrated in one single-dose study (Study 1) and one multiple-dose study (Study 2) in the treatment of established neonatal RDS involving approximately 500 infants. Each study was randomized, multicenter, and controlled. REFER TO PACKAGE INSERT FOR STUDY DESCRIPTION RESULTS.

ACUTE CLINICAL EFFECTS
As with other surfactants, marked improvements in oxygenation may occur within minutes of the administration of CUROSURF.

WARNINGS
CUROSURF is intended for intratracheal use only.

THE ADMINISTRATION OF EXOGENOUS SURFACTANTS, INCLUDING CUROSURF, CAN RAPIDLY AFFECT OXYGENATION AND LUNG COMPLIANCE. Therefore, infants receiving CUROSURF should receive frequent clinical and laboratory assessments so that oxygen and ventilatory support can be modified to respond to respiratory changes. CUROSURF should only be administered by those trained and experienced in the care, resuscitation, and stabilization of pre-term infants.

TRANSIENT ADVERSE EFFECTS SEEN WITH THE ADMINISTRATION OF CUROSURF INCLUDE BRADYCARDIA, HYPOTENSION, ENDOTRACHEAL TUBE BLOCKAGE, AND OXYGEN DESATURATION. These events require stopping Curosurf administration and taking appropriate measures to alleviate the condition. After the patient is stable, dosing may proceed with appropriate monitoring.

PRECAUTIONS
General
Correction of acidosis, hypotension, anemia, hypoglycemia, and hypothermia is recommended prior to CUROSURF administration.

Surfactant administration can be expected to reduce the severity of RDS but will not eliminate the mortality and morbidity associated with other complications of prematurity.

Sufficient information is not available on the effects of administering initial doses of CUROSURF other than 2.5 mL/kg (200 mg/kg), subsequent doses other than 1.25 mL/kg (100 mg/kg), administration of more than three total doses, dosing more frequently than every 12 hours, or initiating therapy with CUROSURF more than 15 hours after diagnosing RDS. Adequate data are not available on the use of CUROSURF in conjunction with experimental therapies of RDS, e.g., high-frequency ventilation.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
Studies to assess potential carcinogenic and reproductive effects of CUROSURF, or other surfactants, have not been conducted.

Mutagenicity studies of CUROSURF, which included the Ames test, gene mutation assay in Chinese hamster V79 cells, chromosomal aberration assay in Chinese hamster ovarian cells, unscheduled DNA synthesis in HELA S3 cells, and *in vivo* mouse nuclear test, were negative.

ADVERSE REACTIONS
Transient adverse effects seen with the administration of CUROSURF include bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation.

The rates of common complications of prematurity observed in Study 1 are shown below in Table 3.

TABLE 3
COMPLICATIONS OF PREMATURITY

	CUROSURF 2.5 mL/kg (200 mg/kg) n=78 %	CONTROL* n=66 %
Acquired Pneumonia	17	21
Acquired Septicemia	14	18
Bronchopulmonary Dysplasia	18	22
Intracranial Hemorrhage	51	64
Patent Ductus Arteriosus	60	48
Pneumothorax	21	36
Pulmonary Interstitial Emphysema	21	38

*Control patients were disconnected from the ventilator and manually ventilated for 2 minutes. No surfactant was instilled.

Immunological studies have not demonstrated differences in levels of surfactant-anti-surfactant immune complexes and anti-CUROSURF antibodies between patients treated with CUROSURF and patients who received control treatment.

OVERDOSAGE
There have been no reports of overdosage following the administration of CUROSURF.

In the event of accidental overdosage, and only if there are clear clinical effects on the infant's respiration, ventilation, or oxygenation, as much of the suspension as possible should be aspirated and the infant should be managed with supportive treatment, with particular attention to fluid and electrolyte balance.

Dosing Precautions
Transient episodes of bradycardia, decreased oxygen saturation, reflux of the surfactant into the endotracheal tube, and airway obstruction have occurred during the dosing procedure of CUROSURF. These events require interrupting the administration of CUROSURF and taking the appropriate measures to alleviate the condition. After stabilization, dosing may resume with appropriate monitoring.

HOW SUPPLIED
CUROSURF® (poractant alfa) Intratracheal Suspension (NDC Numbers: 49502-180-01 [1.5 mL]; 49502-180-03 [3 mL]) is available in sterile, ready-to-use rubber-stoppered clear glass vials containing 1.5 mL (120 mg phospholipids) or 3 mL (240 mg phospholipids) of suspension. One vial per carton.

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SpO_2 System	Masimo SET	OXISMART XL N-395	N-200
True Hypoxemias Missed	2%	37%	47%
False Alarms	7%	18%	57%

Source: Barker SJ, Morgan S. Effects of Motion on the Performance of Five Pulse Oximeters. Presented in poster form at the Society for Technology in Anesthesiology (STA) meeting in Orlando, FL, January 2001.

low perfusion study

SpO_2 System	Masimo SET	OXISMART N-295	N-200
True Hypoxemias Missed	0%	33.3%	33.3%
Drop Out Rate	0.8%	9.9%	17.8%

Source: Barker SJ, Nowak S, Morgan S. The Performance of Three Pulse Oximeters During Low Perfusion in Volunteers. Anesthesiology 1997;87(3A):A34.

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SPECIAL ISSUE

CONSENSUS CONFERENCE ON AEROSOLS AND DELIVERY DEVICES

CO-CHAIRS

Myrna A Dolovich PEng
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Distribution of Pulmonary Blood Flow—West JB. Am J Respir Crit Care Med 1999 Dec 1;160(6):1802–1803.

Perfluorocarbon Fluid As a Mediator of Pulmonary Barotrauma: A Potential Hazard of Liquid Ventilation—Demers B. Chest 2000 Jan;117(1):8–10.

Knowledge and Beliefs of Samples of the General Population about Asthma—Charpin D, Ramadour M, Lanteaume A, Vervloet D. Chest 2000 Jan;117(1):292–294.

Assessment of Regional Tissue Oxygenation (review)—Siegemund M, van Bommel J, Ince C. Intensive Care Med 1999 Oct;25(10):1044–1060.

New Insights in Mechanical Ventilation for Pediatric Patients (review)—Calderini E. Intensive Care Med 1999 Oct;25(10):1194–1196.

Assisted Ventilation for Chronic Neuromuscular Disorders—Road JD. Thorax 2000 Jan; 55(1):1–2.

Transtracheal Air in the Treatment of Obstructive Sleep Apnoea Hypopnoea Syndrome—Series F, Forge JL, Lampron N, Cormier Y. Thorax 2000 Jan;55(1):86–87.

Maintaining Spontaneous Breathing Efforts During Mechanical Ventilatory Support (editorial)—Kuhlen R, Putensen C. Intensive Care Med 1999 Nov;25(11):1203–1205.

Staffing Intensity, Skill Mix and Mortality Outcomes: The Case of Chronic Obstructive Lung Disease—Robertson RH, Hassan M. Health Serv Manage Res 1999;12(4):258-268.

The hospital re-engineering movement has resulted in major changes in hospital staffing. These staffing changes have the potential to reduce staffing intensity and skill mix, both generally and within specific caregiver groups. Prior research has shown that both skill mix and staffing intensity are positively associated with outcomes indicative of the quality of hospital care. This study extends beyond prior research and expanding the scope of staffing intensity and skill mix measures beyond that of physicians and nursing personnel and by focusing on a specific diagnostic group, patients with chronic obstructive pulmonary disease (COPD). Multiple regression analysis was performed using the 30-day post-admission observed mortality rate for Medicare patients being treated for COPD relative to the predicted rate as the dependent variable. Analyses were repeated for 1989, 1990 and 1991. Among the explanatory variables were staffing intensity measures for health care workers that were thought to contribute significantly to the care needed by patients with COPD. The results indicate that the only group of health care workers which showed staffing intensities positively associated with better outcomes in this group of patients was respiratory care practitioners, respiratory therapists and respiratory therapy technicians. The results relative to skill mix were inconclusive. It was concluded that during the 1989-1991 period, hospitals with higher staffing intensities for both respiratory therapists and respiratory therapy technicians had better outcomes for their Medicare inpatients being treated for COPD.

Ventilation with Lower Tidal Volumes As Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000;342(18):1301–1308.

BACKGROUND: Traditional approaches to mechanical ventilation use tidal volumes of 10 to 15 mL per kilogram of body weight and may cause stretch-induced lung injury in patients with acute lung injury and the acute respiratory distress syndrome. We therefore conducted a trial to determine whether ventilation with lower tidal volumes would improve the clinical outcomes in these patients. METHODS: Patients with acute lung injury and the acute respiratory distress syndrome were enrolled in a multicenter, randomized trial. The trial compared traditional ventilation treatment, which involved an initial tidal volume of 12 mL per kilogram of predicted body weight and an airway pressure measured after a 0.5-second pause at the end of inspiration (plateau pressure) of 50 cm of water or less, with ventilation with a lower tidal volume, which involved an initial tidal volume of 6 mL per kilogram of predicted body weight and a plateau pressure of 30 cm of water or less. The primary outcomes were death before a patient was discharged home and was breathing without assistance and the number of days without ventilator use from day 1 to day 28. RESULTS: The trial was stopped after the enrollment of 861 patients because mortality was lower in the group treated with lower tidal volumes than in the group treated with traditional tidal volumes (31.0 percent vs. 39.8 percent, p=0.007), and the number of days without ventilator use during the first 28 days after randomization was greater in this group (mean [±SD], 12±11 vs. 10±11; p=0.007). The mean tidal volumes on days 1 to 3 were 6.2±0.8 and 11.8±0.8 mL per kilogram of

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1. Dalby RN, et al. Evaluation of aerosol drug output from the OptiChamber® and AeroChamber® spacers in a model system. *J Asthma* 35(2), 171-175, 1998.
2. Beihn R, et al. Comparative respiratory deposition of ^{99m}Tc labeled particles of albuterol using a metered dose inhaler, a metered dose inhaler with AeroChamber® spacer and OptiChamber® spacer in healthy human volunteers using gamma-scintigraphy, 1997 (Data on file, Respironics, Inc.).
3. Data on file, Respironics, Inc.

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predicted body weight ($p<0.001$), respectively, and the mean plateau pressures were 25±6 and 33±8 cm of water ($p<0.001$), respectively. CONCLUSIONS: In patients with acute lung injury and the acute respiratory distress syndrome, mechanical ventilation with a lower tidal volume than is traditionally used results in decreased mortality and increases the number of days without ventilator use.

Long Term Non-Invasive Ventilation in the Community for Patients with Musculoskeletal Disorders: 46 Year Experience and Review—Baydur A, Layne E, Aral H, Krishnareddy N, Topacio R, Frederick G, Bodden W. Thorax 2000 Jan;55(1):4-11.

BACKGROUND: A study was undertaken to assess the long term physiological and clinical outcome in 79 patients with musculoskeletal disorders (73 neuromuscular, six of the chest wall) who received non-invasive ventilation for chronic respiratory failure over a period of 46 years. METHODS: Vital capacity (VC) and carbon dioxide tension (P_{CO_2}) before and after initiation of ventilation, type and duration of ventilatory assistance, the need for tracheostomy, and mortality were retrospectively studied in 48 patients who were managed with mouth/nasal intermittent positive pressure ventilation (M/NIPPV) and 31 who received body ventilation. The two largest groups analysed were 45 patients with poliomyelitis and 15 with Duchenne's muscular dystrophy. Twenty five patients with poliomyelitis received body ventilation (for a mean of 290 months) and 20 were supported by M/NIPPV (mean 38 months). All 15 patients with Duchenne's muscular dystrophy were ventilated by NIPPV (mean 22 months). RESULTS: Fourteen patients with poliomyelitis on body ventilation (56%) but only one on M/NIPPV, and 10 of 15 patients (67%) with Duchenne's muscular dystrophy eventually received tracheostomies for ventilatory support. Five patients with other neuromuscular disorders required tracheostomies. Twenty of 29 tracheostomies (69%) were provided because of progressive disease and hypercarbia which could not be controlled by non-invasive ventilation; the remaining nine were placed because of bulbar dysfunction and aspiration related complications. Nine of 10 deaths occurred in patients on body ventilation (six with poliomyelitis), although the causes of death were varied and not necessarily related to respiratory complications. A proportionately greater number of patients on M/NIPPV (67%) reported positive outcomes (improved sense of wellbeing and independence) than did those on body ventilation (29%, $p<0.01$). However, other than tracheostomies and deaths, negative outcomes in the form of machine/interface discomfort and self-discontinuation of ventilation also occurred at a rate 2.3 times higher than in the group who received body ventilation. None of the six patients with chest wall disorders (all on M/NIPPV) required tracheostomy or died. Hospital admission rates increased nearly eightfold in patients receiving body ventilation (all poliomyelitis patients) compared with before ventilation ($p<0.01$) while in those supported by M/NIPPV they were reduced by 36%. CONCLUSIONS: Non-invasive ventilation (NIV) in the community over prolonged periods is a feasible although variably tolerated form of management in patients with neuromuscular disorders. While patients who received body ventilation were followed the longest (mean 24 years), the need for tracheostomy and deaths occurred more often in this group (most commonly in the poliomyelitis patients). Despite a number of discomforts associated with M/NIPPV, a larger proportion of patients experienced improved wellbeing, independence, and ability to perform daily activities.

Biological Quality Control for Exercise Testing—Revill SM, Morgan MD. Thorax 2000 Jan;55(1):63-66.

BACKGROUND: A study was undertaken to evaluate the use of a biological quality control programme for a computer controlled, breath-by-breath exercise test system over a 2.5 year period. METHODS: One healthy volunteer performed a regular progressive treadmill test with breath-by-breath measurements of oxygen uptake ($\dot{V}_{O_2}$), carbon dioxide output ($\dot{V}_{CO_2}$), ventilation ($\dot{V}_E$), and the ECG heart rate (HR). Following a familiarisation period, five consecutive tests were performed and the measurements at peak exercise were averaged to give baseline values. All tests were compared with these values. RESULTS: A total of 35 tests were recorded. The within subject standard deviation for measurements at peak exercise were 52 mL/min for $\dot{V}_{O_2}$, 74 mL/min for $\dot{V}_{CO_2}$, 3.1 L/min for $\dot{V}_E$, and 3 beats/min for HR. The mean (SE) percentage variation in measurements at peak exercise compared with the baseline values was +0.37 (0.30)% for $\dot{V}_{O_2}$, -0.10 (0.39)% for $\dot{V}_{CO_2}$, -0.88 (0.52)% for $\dot{V}_E$, and +1.2 (0.26)% for HR. The variability present in measurements made during high and moderate intensity exercise (73% $\dot{V}_{O_2}$ peak) was not significantly different ($p>0.05$). During the study period the quality control detected a fault on the oxygen analyser which was not apparent from the automatic calibration. CONCLUSIONS: Regular quality control using a healthy volunteer allows all components of the breath-by-breath system to be checked simultaneously and in a manner which is consistent with its clinical use. This practice can highlight faults not detected by automatic calibration.

Supplemental Perioperative Oxygen to Reduce the Incidence of Surgical-Wound Infection—Outcomes Research Group. Greif R, Akca O, Horn EP, Kurz A, Sessler DI. N Engl J Med 2000 Jan 20;342(3):161-167.

BACKGROUND: Destruction by oxidation, or oxidative killing, is the most important defense against surgical pathogens and depends on the partial pressure of oxygen in contaminated tissue. An easy method of improving oxygen tension in adequately perfused tissue is to increase the concentration of inspired oxygen. We therefore tested the hypothesis that the supplemental administration of oxygen during the perioperative period decreases the incidence of wound infection. METHODS: We randomly assigned 500 patients undergoing colorectal resection to receive 30% or 80% inspired oxygen during the operation and for two hours afterward. Anesthetic treatment was standardized, and all patients received prophylactic antibiotic therapy. With use of a double-blind protocol, wounds were evaluated daily until the patient was discharged and then at a clinic visit two weeks after surgery. We considered wounds with culture-positive pus to be infected. The timing of suture removal and the date of discharge were determined by the surgeon, who did not know the patient's treatment-group assignment. RESULTS: Arterial oxygen saturation was normal in both groups; however, the arterial and subcutaneous partial pressure of oxygen was significantly higher in the patients given 80% oxygen than in those given 30 percent oxygen. Among the 250 patients who received 80% oxygen, 13 (5.2%; 95% confidence interval, 2.4 to 8.0%) had surgical-wound infections, as compared with 28 of the 250 patients given 30% oxygen (11.2%; 95% confidence interval, 7.3 to 15.1%; $p=0.01$). The absolute difference between groups was 6.0% (95% confidence interval, 1.2 to 10.8%). The duration of hospitalization was similar in the two groups. CONCLUSIONS: The perioperative administration of supplemental oxygen is a practical method of reducing the incidence of surgical-wound infections.

Trends in Pregnancy-Related Smoking Rates in the United States, 1987-1996—Ebrahim SH, Floyd RL, Merritt RK 2nd, Decoufle P, Holtzman D. JAMA 2000 Jan 19;283(3):361-366.

CONTEXT: Rates of smoking are increasing among adolescents and young adults, but trends in smoking among pregnant women have not been studied. OBJECTIVE: To assess pregnancy-related variations in smoking behaviors and their determinants among women of childbearing age in the United States. DESIGN: Analysis of data collected between 1987-1996 from the Behavioral Risk Factor Surveillance System survey. SETTING AND SUBJECTS: A total of 187302 (178499 nonpregnant and 8803 pregnant) noninstitutionalized women aged 18 to 44 years from 33 states. MAIN OUTCOME MEASURES: Prevalence rates of smoking

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initiation and current smoking, median number of cigarettes smoked, and adjusted odds ratios for smoking stratified by pregnancy status; prevalence rate ratio for current smoking comparing pregnant with nonpregnant women. RESULTS: The overall percentage of women who had ever initiated smoking decreased significantly from 44.1% in 1987 to 38.2% in 1996. During that 10-year period, the prevalence of current smoking also decreased significantly among both pregnant women (16.3% to 11.8%) and nonpregnant women (26.7% to 23.6%). Overall, pregnant women were about half (54%) as likely as nonpregnant women to be current smokers during 1987-1996. Over time, the median number of cigarettes smoked per day by pregnant smokers remained at 10, whereas among nonpregnant smokers it decreased from 19 to 15 ($p< 0.05$ for trend). In the same period, among young women (aged 18-20 years), prevalence rates of smoking initiation and current smoking increased slightly. Sociodemographic subgroups of women at increased risk for current smoking were the same for pregnant and nonpregnant women (ie, those with a completed high school education or less, whites, and those who were unmarried). CONCLUSIONS: In this analysis, the decline in smoking over time among pregnant women was primarily due to the overall decline in smoking initiation rates among women of childbearing age, not to an increased rate of smoking cessation related to pregnancy. To foster effective perinatal tobacco control, efforts are needed to further reduce the number of young women who begin smoking. Clinicians should query all pregnant women and women of childbearing age about smoking and provide cessation and relapse interventions to each smoker.

Bronchodilator Delivery by Metered-Dose Inhaler in Mechanically Ventilated COPD Patients: Influence of Tidal Volume—Mouloudi E, Katsanoulas K, Anastasaki M, Hoing S, Georgopoulos D. Intensive Care Med 1999 Nov;25(11):1215-1221.

OBJECTIVE: The delivery of bronchodilator drugs with metered-dose inhaler (MDI) and a spacer in mechanically ventilated patients has become a widespread practice. However, the various ventilator settings that influence the efficacy of MDI are not well established. The tidal volume (V_T) during drug delivery has been suggested as one of the factors that might increase the effectiveness of this therapy. To test this, the effect of two different V_T on the bronchodilation induced by β2-agonists administered with MDI and a spacer in a group of mechanically ventilated patients with chronic obstructive pulmonary disease (COPD) was examined. METHODS: Nine patients with COPD, mechanically ventilated on volume-controlled mode, were prospectively randomised to receive six puffs of salbutamol (S, 100 micrograms/puff) either with a V_T of 8 mL/kg (normal V_T, 582 ± 85) or with a V_T of 12 mL/kg (high V_T, 912 ± 137). With both modes inspiratory flow was identical. S was administered with an MDI adapted to the inspiratory limb of the ventilator circuit using an aerosol cloud enhancer spacer. After a 6-h washout, patients were crossed-over to receive S by the alternative mode of administration. Static and dynamic airway pressures, minimum (Rint) and maximum (Rrs) inspiratory resistance, the difference between Rrs and Rint (Δ R), static end-inspiratory respiratory system compliance (Cst,rs), intrinsic positive end-expiratory pressure (PEEPi) and heart rate (HR) were measured before and at 15, 30 and 60 min after S. RESULTS: S caused a significant decrease in dynamic and static airway pressures, PEEPi, Rint and Rrs. These changes were not influenced by V_T and were evident at 15, 30 and 60 min after S. With normal and high V_T, Cst,rs, Δ R and HR did not change after S. CONCLUSIONS: We conclude that S delivered with an MDI and a spacer device induces significant bronchodilation in mechanically ventilated patients with COPD, the magnitude of which is not affected by at least a 50% increase in V_T. These results do not support the V_T manipulations when bronchodilators are administered in adequate doses during controlled mechanical ventilation.

Effects of Prone Position on Alveolar Recruitment and Oxygenation in Acute Lung Injury—Guerin C, Badet M, Rosselli S, Heyer L, Sab JM, Langevin B, et al. Intensive Care Med 1999 Nov;25(11):1222-1230.

OBJECTIVE: To investigate the effects of prone position (PP) on alveolar recruitment and oxygenation in acute respiratory failure. DESIGN: Prospective physiologic study. SETTING: Medical ICU two in a university hospital. PATIENTS: Twelve adult patients intubated and mechanically ventilated with medical primary acute lung injury/adult respiratory distress syndrome (ALI/ARDS) in whom PP was indicated. MEASUREMENTS AND RESULTS: We constructed the static inflation volume-pressure curves (V-P) of the respiratory system in the 12 patients and differentiated between lung and chest wall in ten of them. We determined the difference between end-expiratory lung volume on positive end-expiratory pressure (PEEP) and relaxation volume of the respiratory system on zero PEEP (Δ FRC). The recruited alveolar volume was computed as the Δ FRC times the ratio of static elastance of the respiratory system to the lung. These measurements together with arterial blood gases determination were made in supine position (SP1), after 1 h of PP and after 1 h of supine repositioning (SP2) at the same level of PEEP. The P_{aO_2}/F_{IO_2} ratio improved from SP1 to PP (136 $\pm$ 17 vs 204 $\pm$ 24 mm Hg; $p < 0.01$). An PP-induced alveolar recruitment was found in five patients. The change in oxygenation correlated to the recruited volume. The static elastance of the chest wall decreased from 4.62 $\pm$ 0.99 cm H_2O/L in SP1 to 6.26 $\pm$ 0.54 cmH_2O/L in PP ($p < 0.05$) without any correlation to the change in oxygenation. CONCLUSIONS: Alveolar recruitment may be a mechanism of oxygenation improvement in some patients with acute hypoxemic respiratory failure. No correlation was found between change in oxygenation and chest wall elastic properties.

Changing a Hydrophobic Heat and Moisture Exchanger After 48 Hours Rather Than 24 Hours: A Clinical and Microbiological Evaluation—Boisson C, Viviand X, Arnaud S, Thomachot L, Miliani Y, Martin C. Intensive Care Med 1999 Nov;25(11):1237-1243.

OBJECTIVE: Complications following ventilation with dry and cold gases may be prevented by the use of artificial noses or heat and moisture exchangers, which are a solution to both the problems of humidification and heat preservation. The aim of the present study was to determine whether changing hydrophobic heat and moisture exchangers (HMEs) every 48 h rather than 24 h would affect their efficacy to preserve the heat and moisture of inspiratory gases. The impact of a prolonged use of the HME on its microbial colonization was also assessed. DESIGN: Prospective observational study. SETTING: ICU of a university hospital. PATIENTS: Twelve patients requiring controlled mechanical ventilation for more than 2 days were evaluated. INTERVENTIONS: The patients were ventilated with a heat and moisture exchanger (HME) (Maxipleat Filter, Europe Medical, France). The hydrophobic HME was placed between the Y-piece and the connecting tube and changed after 48 h of continuous use. Temperature (degree C), relative humidity (%) and absolute humidity (mg H_2O/L) were obtained using the capacitive sensor principle. Bacterial colonization (tracheal secretions and ventilator side of the HME) were obtained on days 1 and 2. MEASUREMENTS AND RESULTS: After 48 h of ventilation with the same HME, tracheal tube occlusion was never observed. Using the same hydrophobic HME for 48 h rather than 24 h did not affect its technical performance: temperature at 24 h: 32.5 $\pm$ 1.3 degrees C, at 48 h: 32.7 $\pm$ 1.8 degrees C; relative humidity (RH) at 24 h: 99.0 $\pm$ 1.4%, at 48 h: 99.0 $\pm$ 1.4%; absolute humidity (AH) at 24 h: 34.0 $\pm$ 2.4 mg H_2O/L, at 48 h: 34.4 $\pm$ 3.5 mg H_2O/L. Peak and mean airway pressures did not change over the 48-h study period, with identical tidal and minute volumes in the study patients. Total respiratory heat losses were not modified during the 48-h study period (at 24 h: 152 $\pm$ 47 cal/min, at 48 h: 149 $\pm$ 65 cal/min). Evaporative and convective heat losses were not modified either. On day 1, eight patients had positive cultures of their tracheal secretions at a colony count of 10^3 or higher cfu/mL. After 48 h of use of the same HME, only six patients had a positive culture of their tracheal secretions. Cultures from the ventilator sides of the HMEs were all sterile (12/12) after 48 h of use. CONCLUSIONS: Changing the hydrophobic HME after 48 h rather than 24 h did not affect its technical performance in terms of heat and water preservation of ventilatory gases. There is also some indirect evidence of very little, if any, change in HME resistance. No bacterial colonization of the ventilator sides of the HMEs was observed after 48 h of use. However, other large clinical trials should be undertaken to confirm the safety of extending the time between HME changes.

Safety and Efficacy of a Sustained Inflation for Alveolar Recruitment in Adults with Respiratory Failure—Lapinsky SE, Aubin M, Mehta S, Boiteau P, Slutsky AS. Intensive Care Med 1999 Nov;25(11): 1297-1301.

OBJECTIVE: To assess the safety and efficacy of a sustained inflation, used as a lung volume recruitment maneuver in ventilated patients with hypoxemic respiratory failure. DESIGN: Prospective data collection as part of a quality assurance program following introduction of a lung volume recruitment guideline in the intensive care unit. SETTING: Academic medical-surgical critical care unit. PATIENTS: Hypoxemic patients with bilateral pulmonary infiltrates. Patients with chronic obstructive pulmonary disease, pulmonary barotrauma and hemodynamic instability were excluded. INTERVENTIONS: A sustained inflation using a pressure of 30 to 45 cm H_2O was applied for 20 s. The pressure was determined as the lesser of 45 cm H_2O or the peak pressure while ventilated at a tidal volume of 12 mL/kg. Intra-arterial blood pressure and pulse oximetry were monitored continuously. MEASUREMENTS AND RESULTS: Significant improvement in oxygenation occurred in the majority of patients within 10 min. The mean oxygen saturation improved from 86.9 $\pm$ 5.5 to 94.3 $\pm$ 2.3% ($p < 0.01$). No significant adverse effects were noted: hypotension and mild oxygen desaturation occurred in some patients during the 20-s inflation, reversing rapidly after inflation was terminated. No barotrauma occurred. CONCLUSIONS: A sustained inflation is a safe, clinically applicable method of lung volume recruitment which improves oxygenation in selected patients and may have a role in ventilatory management.

Results at 1 Year of Outpatient Multidisciplinary Pulmonary Rehabilitation: A Randomised Controlled Trial—Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shiels K, et al. Lancet 2000 Jan 29;355(9201):362-368.

BACKGROUND: Pulmonary rehabilitation seems to be an effective intervention in patients with chronic obstructive pulmonary disease. We undertook a randomised controlled trial to assess the effect of outpatient pulmonary rehabilitation on use of health care and patients' wellbeing over 1 year. METHODS: 200 patients with disabling chronic lung disease (the majority with chronic obstructive pulmonary disease) were randomly assigned a 6-week multidisciplinary rehabilitation programme (18 visits) or standard medical management. Use of health services was assessed from hospital and general-practice records. Analysis was by intention to treat. FINDINGS: There was no difference between the rehabilitation (n=99) and control (n=101) groups in the number of patients admitted to hospital (40 vs 41) but the number of days these patients spent in hospital differed significantly (mean 10.4 [SD 9.7] vs 21.0 [20.7], p=0.022). The rehabilitation group had more primary-care consultations at the general-practitioner's premises than did the control group (8.6 [6.8] vs 7.3 [8.3], p=0.033) but fewer primary-care home visits (1.5 [2.8] vs 2.8 [4.6], p=0.037). Compared with control, the rehabilitation group also showed greater improvements in walking ability and in general and disease-specific health status. INTERPRETATION: For patients chronically disabled by obstructive pulmonary disease, an

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intensive, multidisciplinary, outpatient programme of rehabilitation is an effective intervention, in the short term and the long term, that decreases use of health services.

Emergency Pre-Hospital Management of Patients Admitted with Acute Asthma—Simpson AJ, Matusiewicz SP, Brown PH, McCall IA, Innes JA, Greening AP, Crompton GK. Thorax 2000 Feb;55(2):97-101.

BACKGROUND: Little is known about the management of acute asthma prior to hospital admission. Pre-hospital treatment of patients referred to hospital with acute asthma was therefore studied in 150 patients divided into three groups: those in the Edinburgh Emergency Asthma Admission Service (EEAAS) who can contact an ambulance and present directly to respiratory services when symptoms arise (n = 38), those under continuing supervision at a hospital respiratory outpatient clinic (n = 54), and those managed solely in primary care (n = 58). METHODS: Standardised admission forms detailing aspects of pre-hospital management, case records, GP referral letters, and ambulance patient transport forms were analysed. RESULTS: In each group airflow obstruction had improved upon arrival at hospital, the effect being most marked in patients transported by ambulance ($p<0.001$) and in those receiving nebulised β_2 agonists prior to admission ($p<0.005$). However, 25% of patients arrived without having nebulised β_2 agonists and 37% without having glucocorticoids. EEAAS patients were least likely to receive nebulised β_2 agonists before arrival at hospital ($p<0.05$). This observation was attributable to a tendency for these patients to travel to hospital by car rather than by ambulance. CONCLUSIONS: There is an important shortfall in administration of bronchodilators and glucocorticoids for acute asthma before arrival at hospital. Ambulances equipped with nebulised bronchodilators provide the optimal mode of transport to hospital for patients with acute asthma. In Edinburgh ambulances are not being used by a significant proportion of the population with asthma, possibly because of the mistaken belief that personal transport arrangements reduce journey time to hospital.

Humidification Method that Decreases Condensate Contamination in Ventilator Tubing—Anstan F, Suzukawa M. Heart Lung 2000 Jan-Feb;29(1):56–59.

OBJECTIVE: To demonstrate combining unheated bubble-through humidifier with a heat-moisture exchanger filter for the purpose of decreasing condensate contamination in mechanical ventilator tubing. DESIGN: Single-case, pretest and posttest. SETTING: University-affiliated and nonprofit hospital. PATIENT: A 32-year-old man with Pickwickian syndrome and pneumonia caused by *Pseudomonas aeruginosa* received mechanical ventilation for 14 days. METHODS: Ventilator tubing was cultured in two 24-hour trials, using a pretest and posttest design, to assess tubing bacterial contamination during use of 2 humidification methods. In the first trial, a traditional heated bubble-through humidifier (HBH) was used for 24 hours. Before the start of the second trial, the "wet" tubing and the heated bubble-through humidifier were removed and replaced with clean equipment through the use of aseptic technique. The bubble-through humidifier was placed on the "cold," or unheated mode, and a heat-moisture exchanger filter was attached to the Y-connector of the ventilator tubing. RESULTS: The heated bubble-through humidifier method revealed contamination of the ventilator tubing in 3 places with the patient's strain of *P aeruginosa* in addition to copious water condensate. The unheated bubble-through humidifier/heat moisture exchanger filter method demonstrated no bacterial contamination or condensate in the tubing. CONCLUSION: It can be inferred that the humidification method using the combination of an unheated bubble-through humidifier and a heat moisture exchanger filter has the potential benefit of preventing "reseeding" of the patient's airway with contaminated condensate.

Assessment of Respiratory Function: Influence of Spirometry Reference Values and Normality Criteria Selection—Quadrelli S, Roncoroni A, Montiel G. Respir Med 1999 Aug;93(8):523–535.

The purpose of this study was to determine the impact upon classification of patients of the choice of reference equation and the criterion defining the lower limit of the normal range in clinical practice. One thousand consecutive spirometries were checked to calculate the predicted values [forced vital capacity (FVC) and forced expiratory volume in sec (FEV_1)] in accordance with the equations by Morris, Cherniack, Crapo, Knudson and the Economic Community for Coal and Steel (ECCS). We quantified the difference between the predicted values obtained for each individual and each equation, determined the percentage of individuals whose classification might have changed from normal to abnormal when using a different equation and defined the lower limit of the normal range in accordance with the determination of (1) the 90% confidence interval or (2) 80% of predicted, comparing their differences. The greatest differences found were between the values given by Morris and Crapo's equations for male FEV_1, between Morris and Cherniak for female FEV_1 and male FVC and between Morris and Knudson for female FVC. Using 80% of predicted value for female FEV_1, up to 35% of tests changed their classification from 'normal' to 'abnormal' upon changing the equation used. A high percentage of tests showed a lower limit of normal defined by the confidence interval under 80% and 70% of predicted value. This study emphasizes the importance of choosing the appropriate reference equation. We do not consider it acceptable to use a fixed percentage of the predicted value as the lower limit of normal because of the great number of patients found to be inappropriately classified.

Bedside Procedures. Solutions to the Pitfalls of Intrahospital Transport—Haupt MT, Rehm CG. Crit Care Clin 2000 Jan;16(1):1–6, v.

The technology to perform diagnostic and therapeutic procedures at the bedside continues to advance. Because of documented hazards and the expense of intrahospital transport, the bedside is becoming an appealing site for procedures that are more commonly performed in radiologic, bronchoscopic, other procedural suites, and the operating room.

Fiberoptic Bronchoscopy for Diagnosis and Treatment (review)—Liebler JM, Markin CJ. Crit Care Clin 2000 Jan;16(1):83–100.

Bedside fiberoptic bronchoscopy is a valuable tool in the diagnosis and treatment of various respiratory conditions in critically ill patients. The fiberoptic bronchoscope allows direct airway inspection, facilitating the diagnosis of benign and malignant airway lesions. In addition, pulmonary secretions or tissue samples can be collected using the bronchoscope and techniques that allow sampling of the lower airways with minimal or no upper airway contamination. Collection of lower airway samples is important in the diagnosis of pulmonary infiltrates in immunocompromised patients, in many patients with ventilator-associated pneumonia, and in selected patients with CAP. The fiberoptic bronchoscope can be used for therapeutic interventions, such as insertion of an endotracheal tube, removal of an aspirated foreign body, clearance of tenacious secretions, promotion of hemostasis in patients with hemoptysis, instillation of drugs, and assistance in the placement of tracheobronchial prostheses (i.e., airway stents). If proper preprocedural training and planning are done and the patient is monitored carefully during the procedure, fiberoptic bronchoscopy can be performed quickly and safely at the bedside in most critically ill patients.

Minimally Invasive Surgery: Bedside Tracheostomy and Gastrostomy (review)—Goldman RK. Crit Care Clin 2000 Jan;16(1):113–130.

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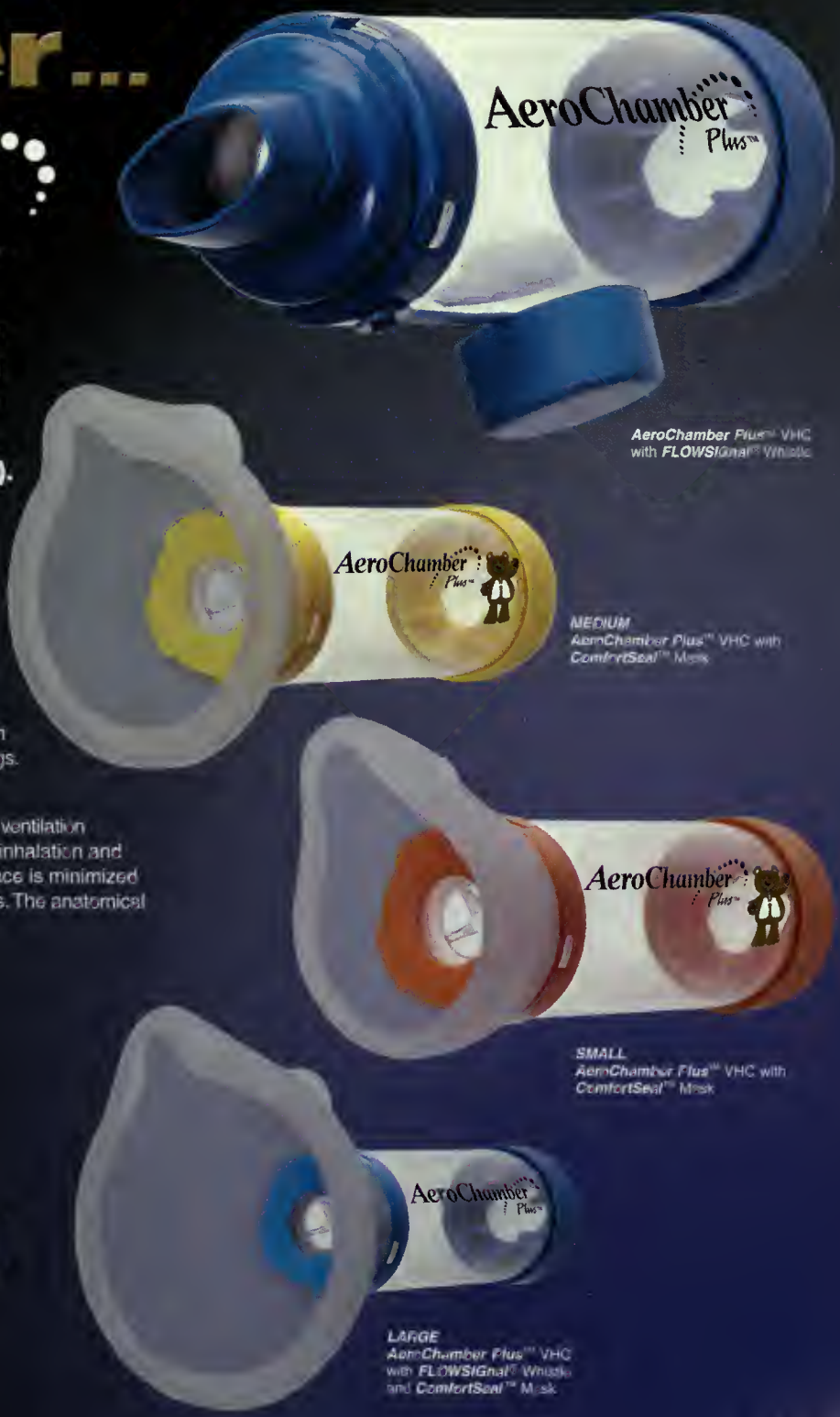
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incisions result in less pain and earlier return to activities. Critically ill patients typically do not benefit from minimally invasive techniques in this manner; however, they do benefit from other aspects of minimally invasive tracheostomy and gastrostomy. Small tracheostomy wounds are associated with reduced wound problems (infection and breakdown). The small stab wounds of minimally invasive gastrostomy are associated with less pain and with an absence of fascial dehiscence. Furthermore, because these procedures are performed easily and safely at the bedside, transport and operating room costs are avoided. Although these procedures are minimally invasive, they are major procedures. Devastating complications can become life-threatening. Attention to detail is required to avoid or respond promptly to complications. In this way, patients receive maximal benefit at minimal risk.

Optimists vs Pessimists: Survival Rate among Medical Patients over a 30-Year Period—Maruta T, Colligan RC, Malinchoc M, Offord KP. Mayo Clin Proc 2000 Feb;75(2):140–143.

OBJECTIVE: To examine explanatory style (how people explain life events) as a risk factor for early death, using scores from the Optimism-Pessimism scale of the Minnesota Multiphasic Personality Inventory (MMPI). SUBJECTS AND METHODS: A total of 839 patients completed the MMPI between 1962 and 1965 as self-referred general medical patients. Thirty years later, the vital status of each of these patients was ascertained. RESULTS: Of the 839 patients, 124 were classified as optimistic, 518 as mixed, and 197 as pessimistic. Follow-up was available for 723 patients. Among these, a 10-point T-score increase on the Optimism-Pessimism scale (e.g., more pessimistic) was associated with a 19% increase in the risk of mortality. CONCLUSION: A pessimistic explanatory style, as measured by the Optimism-Pessimism scale of the MMPI, is significantly associated with mortality.

Nosocomial Tuberculosis Prevention Measures among Two Groups of US Hospitals, 1992 to 1996—Manangan LP, Bennett CL, Tablan N, Simonds DN, Pugliese G, Collazo E, Jarvis WR. Chest 2000 Feb;117(2): 380–384.

OBJECTIVE: To compare trends in nosocomial tuberculosis (TB) prevention measures and health-care worker (HCW) tuberculin skin test (TST) conversion of hospitals with HIV-related *Pneumocystis carinii* pneumonia (PCP) patients and other US hospitals from 1992 through 1996. Design and setting: Surveys in 1992 and 1996 of 38 hospitals with PCP patients in four high-HIV-incidence cities and 136 other US hospitals from the American Hospital Association membership list. PARTICIPANTS: Twenty-seven hospitals with PCP patients and 103 other US hospitals. RESULTS: In 1992, 63% of PCP hospitals and other US hospitals had rooms meeting Centers for Disease Control and Prevention (CDC) criteria (ie, negative air pressure, six or more air exchanges per hour, and air directly vented to the outside) for acid-fast bacilli isolation; in 1996, almost 100% had such isolation rooms. Similarly, in 1992, nonfitted surgical masks were used by HCWs at 60% of PCP hospitals and 68% at other US hospitals, while N95 respirators were used at 90% of PCP hospitals and 83% of other US hospitals in 1996. There was a significant decreasing trend in TST conversion rates among HCWs at both PCP and other US hospitals; however, this trend varied among all hospitals. HCWs at PCP hospitals had a higher risk of TST conversion than those at other US hospitals (relative risk, 1.71; $p < 0.0001$). CONCLUSION: From 1992 through 1996, PCP and other US hospitals have made similar improvements in their nosocomial TB prevention measures and decreased their HCW TST conversion rate. These data show that most hospitals are compliant with CDC TB guidelines even before the enactment of an Occupational Safety and Health Administration TB standard.

Perceptions of Asthma by Adolescents at Home—Rietveld S, Everaerd W. Chest 2000 Feb;117(2):434–439.

OBJECTIVES: To test symptom perception in asthma under natural circumstances and to establish relationships between changes in airway obstruction as indicated by wheeze, dyspnea, general sensations, and emotional state. DESIGN: Continuous in vivo monitoring. METHOD: Symptom perception was tested in 30 adolescents with severe, unstable asthma. They were continuously monitored in their homes for 72 h. Symptom perception was defined as the relation between self-reported dyspnea and airway obstruction as evident from audible wheeze. Tracheal sounds were continuously recorded with wireless telemetry for wheeze assessment. Dyspnea was assessed four times per day on a Likert-type 10-point scale, as well as four times randomly after pager remote command. The subjects kept records of use of medication, daily activities, general symptoms, and mood state in a diary. RESULTS: There were nine subjects with one or two wheeze episodes, another three subjects with three or four episodes, and one subject with almost continuous wheeze. The presence of wheeze in general related significantly to a rise (from individual baseline) in dyspnea of > 2.5 scale points. Acute wheeze was the best predictor of a rise in dyspnea, but prolonged wheeze correlated significantly with negative mood and general symptoms. CONCLUSION: Patients with prolonged airway obstruction perceived symptoms less well and were more vulnerable to negative effects of asthma than patients with acute onset airway obstruction.

Mechanism of CO_2 Retention in Patients with Neuromuscular Disease—Misuri G, Lanini B, Gigliotti F, Iandelli I, Pizzi A, Bertolini MG, et al. Chest 2000 Feb;117(2):447–453.

BACKGROUND: In many studies of patients with muscle weakness, chronic hypercapnia has appeared to be out of proportion to the severity of muscle disease, indicating that factors other than muscle weakness are involved in CO_2 retention. In patients with COPD, the unbalanced inspiratory muscle loading-to-strength ratio is thought to trigger the signal for the integrated response that leads to rapid and shallow breathing and eventually to chronic hypercapnia. This mechanism, although postulated, has not yet been assessed in patients with muscular dystrophy. SUBJECTS: Twenty consecutive patients (mean age, 47.6 years; range, 23 to 67 years) were studied: 11 patients with limb-girdle dystrophy, 3 with Duchenne muscular dystrophy, 1 with Charcot-Marie-Tooth syndrome, 1 with Becker muscular dystrophy, 1 with myotonic dystrophy, 1 with facioscapulohumeral dystrophy, and 2 with amyotrophic lateral sclerosis, without any respiratory complaints. Seventeen normal subjects matched for age and sex were studied as a control group. METHODS: Routine spirometry and arterial blood gases, maximal inspiratory and expiratory muscle pressures (MIP and MEP, respectively), and pleural pressure during maximal sniff test (Pplsn), were measured. Mechanical characteristics of the lung were assessed by evaluating lung resistance (R_L) and dynamic elastance (El_{dyn}). El_{dyn} was assessed as absolute value and as percent of Pplsn; El_{dyn} (%Pplsn) indicates the elastic load per unit of inspiratory muscle force. Breathing pattern was assessed in terms of time (inspiratory time [T_I]; respiratory frequency [R_f]) and volume (tidal volume [V_T]) components of the respiratory cycle. RESULTS: A rapid shallow breathing pattern, as indicated by a greater R_f/V_T ratio and a lower T_I, was found in study patients compared to control subjects. El_{dyn} was greater in study patients, while MIP, MEP, and Pplsn were lower. P_{aCO_2} inversely related to V_T, T_I, and Pplsn ($p = 0.012$, $p = 0.019$, and $p = 0.002$, respectively), whereas it was directly related to R_f, R_f/V_T, El_{dyn}, and El_{dyn} (%Pplsn) ($p < 0.004$ to $p < 0.0001$). Also El_{dyn} (%Pplsn) inversely related to T_I, and the latter positively related to V_T. In other words, increase in El_{dyn} (%Pplsn) was associated with decrease in T_I, and the latter was associated with lower V_T and greater P_{aCO_2}. Mechanical and breathing pattern variables were introduced in a stepwise multiple regression that selected El_{dyn} (%Pplsn) ($p < 0.0001$; $r^2 = 0.62$) as a unique independent predictor of P_{aCO_2}. CONCLUSIONS: The present study shows that in patients with neuromuscular disease, elastic load and

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respiratory muscle weakness are responsible for a rapid and shallow breathing pattern leading to chronic CO_2 retention.

The Effect of Respiratory Therapist-Initiated Treatment Protocols on Patient Outcomes and Resource Utilization—Kollef MH, Shapiro SD, Clinkscale D, Cracchiolo L, Clayton D, Wilner R, Hossin L. Chest 2000 Feb;117(2):467–475.

CONTEXT: Physicians frequently prescribe respiratory treatments to hospitalized patients, but the influence of such treatments on clinical outcomes is difficult to assess. OBJECTIVE: To compare the clinical outcomes of patients receiving respiratory treatments managed by respiratory care practitioner (RCP)-directed treatment protocols or physician-directed orders. DESIGN: A single center, quasi-randomized, clinical study. SETTING: Three internal medicine firms from an urban teaching hospital. PATIENTS: Six hundred ninety-four consecutive hospitalized non-ICU patients ordered to receive respiratory treatments. Main outcome measures: Discordant respiratory care orders, respiratory care charges, hospital length of stay, and patient-specific complications. Discordant orders were defined as written orders for respir-atory treatments that were not clinically indicated as well as orders omitting treatments that were clinically indicated according to protocol-based treatment algorithms. RESULTS: Firm A patients (n = 239) received RCP-directed treatments and had a statistically lower rate of discordant respiratory care orders (24.3%) as compared with patients receiving physician-directed treatments in firms B (n = 205; 58.5%) and C (n = 250; 56.8%; $p < 0.001$). No statistically significant differences in patient complications were observed. The average number of respir-atory treatments and respiratory care charges were statistically less for firm A patients (10.7 ± 13.7 treatments; $868 ± 1,519) as compared with patients in firms B (12.4 ± 12.7 treatments, $1,124 ± 1,339) and C (12.3 ± 13.4 treatments, $1, 054 ± 1,346; $p = 0.009$ [treatments] and $p < 0.001$ [respiratory care]). CONCLUSIONS: Respiratory care managed by RCP-directed treatment protocols for non-ICU patients is safe and showed greater agreement with institutional treatment algorithms as compared with physician-directed respiratory care. Additionally, the overall utilization of respiratory treatments was significantly less among patients receiving RCP-directed respiratory care.

Assessment of Prognosis in Patients with Community-Acquired Pneumonia Who Require Mechanical Ventilation—Pascual FE, Matthay MA, Bacchetti P, Wachter RM. Chest 2000 Feb;117(2):503–512.

Study objectives: Knowing that mortality is high in patients who require mechanical ventilation patients with community-acquired pneumonia (CAP), we hypothesized that the severity of acute lung injury could be used along with nonpulmonary factors to identify patients with the highest risk of death. We formulated a prediction model to quantitate the risk of hospital mortality in this population of patients. DESIGN: Historical prospective study using data collected over the first 24 h of mechanical ventilation. We utilized a hypoxemia index-(1 - lowest [P_{aO_2}/P_{AO_2}]) × [minimum fraction of inspired oxygen to maintain P_{aO_2} at > 60 mm Hg] × 100), where P_{AO2} is the alveolar partial pressure of oxygen-to grade the severity of acute lung injury on a scale from 0 to 100. SETTING: Tertiary care university hospital ICU. PATIENTS: One hundred forty-four adult patients mechanically ventilated for respiratory failure caused by CAP. Measurements and results: Hospital mortality was 46% (n = 66). Multivariate logistic regression analysis revealed five independent predictors of hospital mortality: (1) the extent of lung injury assessed by the hypoxemia index; (2) the number of nonpulmonary organs that failed; (3) immunosuppression; (4) age > 80 years; and (5) medical comorbidity with a prognosis for survival < 5 years. At a 50% mortality threshold, the prediction model correctly classified outcome in 88% of cases. All patients with > 95% predicted probability of death died in hospital. CONCLUSIONS: Based on clinical parameters measured over the first 24 h of mechanical ventilation, this model accurately identified critically ill, mechanically ventilated patients with CAP for whom prolonged intensive care may not be of benefit.

Topical Antibiotics on Tracheostoma Prevents Exogenous Colonization and Infection of Lower Airways in Children—Morar P, Makura Z, Jones A, Baines P, Selby A, Hughes J, van Saene R. Chest 2000 Feb;117(2):513–518.

INTRODUCTION: Patients requiring long-term ventilation are at high risk of lower airway infections, generally of endogenous development. Patients on long-term ventilation, in particular via a tracheostomy, may develop tracheobronchitis or pneumonia of exogenous pathogenesis, ie, caused by microorganisms not carried in the oropharynx. The frequency of exogenous colonization or infection has previously been reported to be as high as 33%. A prospective observational cohort study of 2 years was undertaken to evaluate the efficacy of topical antibiotics in the prevention of exogenous colonization or infection of the lower airways. The antibiotic combination of polymyxin E and tobramycin in a 2% paste was applied four times a day on the tracheostoma. MATERIALS AND METHODS: A total of 23 children (median age, 4.1 months; range, 0 to 215 months) were enrolled in the study from September 1, 1996, until August 30, 1998. Surveillance samples of the oropharynx were obtained before tracheostomy and thereafter twice weekly. Diagnostic samples of the lower airways were taken once weekly and on clinical indication. RESULTS: Fourteen children (61%) had a total of 16 episodes of tracheal colonization or infection with 20 potentially pathogenic microorganisms. Only one child had tracheobronchitis with *Streptococcus pneumoniae* and *Haemophilus influenzae* during the 2-year study. Of the 16 colonization episodes, 12 (75%) were of primary endogenous pathogenesis, ie, caused by microorganisms present in the oropharynx at the time of tracheostomy. Community microorganisms including *S pneumoniae*, *H influenzae*, *Moraxella (Branhamella) catarrhalis*, and *Staphylococcus aureus* were the predominating bacteria. Three patients acquired nosocomial bacteria *Pseudomonas aeruginosa* and *Hafnia alvei* in the oropharynx, subsequently followed by secondary colonization of the lower airways. There was one failure of the prophylaxis: one patient (4%) had exogenous colonization with *Pseudomonas pickettii*. CONCLUSION: Topical antibiotics applied to the tracheostoma were found to be effective in reducing the exogenous route of colonization of the lower respiratory tract, compared with clinical experience and the literature. This promising technique requires further evaluation in randomized trials.

Inhaled Corticosteroids for Asthma Therapy: Patient Compliance, Devices, and Inhalation Technique—Cochrane MG, Bala MV, Downs KE, Mauskopf J, Ben-Joseph RH. Chest 2000 Feb;117(2):542–550.

BACKGROUND: Patient compliance, inhalation devices, and inhalation techniques influence the effectiveness of inhaled medications. METHODS: This article presents the results of a systematic literature review of studies measuring compliance with inhaled corticosteroids, measuring inhalation technique with different inhalation devices, and estimating the proportion of inhaled drug that is deposited in the lung. RESULTS: Overall, patients took the recommended doses of inhaled medication on 20 to 73% of days. Frequency of efficient inhalation technique ranged from 46 to 59% of patients. Education programs have been shown to improve compliance and inhalation techniques. The lung deposition achieved with different inhalers depends on particle size as well as inhaler technique. CONCLUSION: This review demonstrates that multiple factors may come between a prescription of an inhaled corticosteroid and the arrival of that medicine at its target organ, the lung.

A Prospective Study of Fever and Bacteremia after Flexible Fiberoptic Bronchoscopy in Children—Picard E, Schwartz S, Goldberg S, Glick T, Villa Y, Kerem E. Chest 2000 Feb;117(2):573–577.

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Study objectives: To assess the incidence of fever and bacteremia after fiberoptic bronchoscopy in immunocompetent children. DESIGN: Prospective study. PATIENTS: Immunocompetent children undergoing fiberoptic bronchoscopy between January 1997 and June 1998. Measurements and results: Ninety-one children were included in the study. Forty-four children (48%) developed fever within 24 h following bronchoscopy. Bacteremia was not detected in any of the cases at the time of the fever. Children who developed fever were younger than those who remained afebrile (mean age, 2.4 ± 3.6 years vs 4.2 ± 3.7 years; $p = 0.025$). In the fever group, 66% of the bronchoscopies were considered abnormal, compared to 45% in the nonfever group ($p = 0.04$). Of the fever group, 40.5% of BAL fluid cultures had significant bacterial growth, significantly higher compared to the nonfever group (13.2%; $p = 0.006$). Of the 80 patients in whom BAL was performed, fever occurred in 52.5% compared to only 18.2% in those who did not have BAL ($p = 0.03$). BAL fluid content of cell count, lipid-laden macrophages, and interleukin-8 were not significantly different in both groups. In a logistic regression analysis, the significant predictors for developing fever were positive bacterial culture (relative risk, 5.1; 95% confidence interval, 1.6 to 16.4; $p = 0.007$) and abnormal bronchoscopic findings (relative risk, 3.1, 95% confidence interval, 1.2 to 8.3; $p = 0.02$). When age < 2 years was included in the model, this factor became highly significant (relative risk, 5.01; 95% confidence interval, 1.83 to 13.75; $p < 0.002$). CONCLUSIONS: Fever following fiberoptic bronchoscopy is a common event in immunocompetent children and is not associated with bacteremia. Risks to develop this complication are age < 2 years, positive bacterial cultures in BAL fluid, and abnormal bronchoscopic findings.

The Invaluable Pressure-Volume Curve—Wagers SS, Bouder TG, Kaminsky DA, Irvin CG. Chest 2000 Feb;117(2):578–583.

We present a case in which the pressure-volume (P-V) curve proved invaluable in the diagnostic workup of a patient. The patient was a 43-year-old man who presented with progressive dyspnea on exertion, restrictive spirometry, exercise desaturation, and an unremarkable CT scan. Because of the unexpected finding of an unremarkable CT scan, we wanted more data assuring the presence of an indication for lung biopsy. Detailed pulmonary function tests, including a P-V curve, were administered. The P-V curve was abnormal, thus prompting a biopsy, which revealed hypersensitivity pneumonitis. In this report, we discuss the use of P-V curves and the clinical presentation of hypersensitivity pneumonitis.

The Impact of COPD on Lung Health Worldwide: Epidemiology and Incidence—Hurd S. Chest 2000 Feb;117(2 Suppl):1S-4S.

Information on the prevalence of COPD was obtained from vital statistics, health interview surveys, hospital charge records, national publications, and the World Health Organization (WHO). These data indicate that COPD is a common disease with implications for global health. In the United States, morbidity caused by COPD is 4%, making COPD the fourth leading cause of death, exceeded only by heart attacks, cancer, and stroke. Internationally, there is substantial variation in death rates possibly reflecting smoking behavior, type and processing of tobacco, pollution, climate, respiratory management, and genetic factors. The Global Obstructive Lung Disease Initiative, initiated by the National Heart, Lung, and Blood Institute and the WHO, aims to raise awareness of the increasing burden of COPD, decrease morbidity and mortality, promote further study of the condition, and implement programs to prevent COPD.

The Economic Burden of COPD—Sullivan SD, Ramsey SD, Lee TA. Chest 2000 Feb;117(2 Suppl):5S-9S.

COPD is one of the leading causes of morbidity and mortality worldwide and imparts a substantial economic burden on individuals and society. Despite the intense interest in COPD among clinicians and researchers, there is a paucity of data on health-care utilization, costs, and social burden in this population. The total economic costs of COPD morbidity and mortality in the United States were estimated at $23.9 billion in 1993. Direct treatments for COPD-related illness accounted for $14.7 billion, and the remaining $9.2 billion were indirect morbidity and premature mortality estimated as lost future earnings. Similar data from another US study suggest that 10% of persons with COPD account for > 70% of all medical care costs. International studies of trends in COPD-related hospitalization indicate that although the average length of stay has decreased since 1972, admissions per 1,000 persons per year for COPD have increased in all age groups > 45 years of age. These trends reflect population aging, smoking patterns, institutional factors, and treatment practices.

Mechanisms in COPD: Differences from Asthma—Barnes PJ. Chest 2000 Feb;117(2 Suppl):10S-14S.

Although considerable progress has been made in understanding the cellular and molecular mechanisms of asthma, much less attention has been paid to COPD. The inflammatory process in COPD is very different from that in asthma, with different inflammatory cells, mediators, inflammatory effects, and response to therapy. Airway inflammation in asthma, characterized by an eosinophilic inflammation affecting all the airways but not lung parenchyma, is linked to airway hyperresponsiveness. In COPD, there is a predominantly neutrophilic inflammation in the airways. Parenchymal destruction is an important irreversible feature and leads to airflow obstruction through dynamic compression. The eosinophilic inflammation in asthma is markedly suppressed by corticosteroids, but they have no appreciable effect on the inflammation in COPD, consistent with a failure of long-term corticosteroids to alter the progression of COPD.

The Importance of Spirometry in COPD and Asthma: Effect on Approach to Management—Celli BR. Chest 2000 Feb;117(2 Suppl): 15S-19S.

COPD is characterized by airflow limitation. The diagnosis is suggested by history and physical examination and is confirmed by spirometry (ie, a low FEV_1 level that is unresponsive to bronchodilators). Once diagnosed, there is no widely accepted staging or severity scoring system. COPD presently is graded using a single measurement such as FEV_1, which, unlike the case with asthma, has a limited role in disease management. A more comprehensive staging system is required incorporating, for example, age, arterial blood gases, dyspnea, body mass index, and distance walked, in addition to FEV_1. These criteria should allow for more evidence-based recommendations for management of this condition. Asthma is an inflammatory disease also characterized by airflow limitation. But in contrast with COPD, the airflow limitation is highly reversible either spontaneously or with therapy. Repeated lung function measurements using portable peak flowmeters have resulted in improved outcomes. Therefore, frequent flow determination is recommended in the routine management of asthma. Treatment with anti-inflammatory agents and close monitoring of lung function should help decrease the morbidity and mortality associated with asthma.

Recommendations for the Management of COPD—Ferguson GT. Chest 2000 Feb;117(2 Suppl):23S-28S.

Three sets of guidelines for the management of COPD that are widely recognized (from the European Respiratory Society [ERS], American Thoracic Society [ATS], and British Thoracic Society [BTS]) are reviewed and compared. None of the documents uses classic evidence-based documentation, and, in many instances, the recommendations are empiric because of a lack of scientific evidence. Overall, there is strong agreement between the documents. All three guidelines recommend in-

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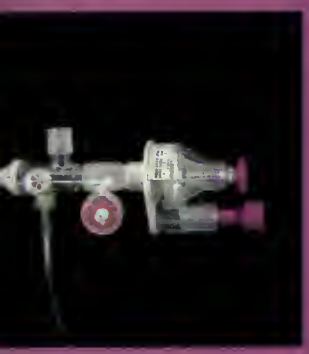

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Program #2
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Presenters: Timothy R. Meyers, BS, RRT and Thomas J. Kallstrom, RRT, FAARC

The prevalence of pediatric asthma has increased dramatically in the last few years. The National Asthma Education and Prevention Program has provided guidelines for management of pediatric asthma. This program will discuss these issues as well as the role of care paths in the management of the disease. Additionally, there have been some significant advances in coping with pediatric asthma in the ER.

Program #3
Drugs, Medications, and Delivery Devices of Importance in Respiratory Care
Videotape Available

Presenters: James B. Fink, MS, RRT, FAARC and David J. Pierson, MD, FAARC

Aerosol therapy is delivered to nearly 80% of respiratory patients. There are a number of new medications in development for both local and systemic administration to those patients. Which device to use, how to negotiate care plans, and how to educate both patients and caregivers are all topics that will be discussed. Perhaps of critical importance is getting the most medication delivered to the patient's lungs, which leads to a discussion of selecting the correct delivery device.

Program #4
Cost-Effective Respiratory Care: You've Got to Change
Videotape Available

Presenters: Kevin L. Shrake, MA, RRT, FACHE, FAAMA, FAARC and Sam P. Giordano, MBA, RRT, FAARC

Practitioners frequently confuse the implementation of protocol treatment and case management. Both programs, if successfully implemented, can lead to cost savings. The problem most practitioners face is how to identify where costs are avoided and resources are conserved. Perhaps most critical is ensuring that the correct care is delivered at the proper time. The health care practitioner is key to the ultimate success of these programs.

Program #5
Pediatric Ventilation: Kids Are Different

Live Videoconference - July 25, 11:30 a.m.-1:00 p.m. Central Time
Teleconference with Videotape - August 15, 11:30 a.m.-12:00 Noon Central Time
Presenters: Mark Heulitt, MD, FAAP, FCCP and Richard D. Branson, BA, RRT

There are significant differences in the anatomy and physiology of the respiratory systems between adults and children, posing problems for the practitioner attempting to mechanically ventilate a pediatric patient. Once the process is underway, the capabilities of the available mechanical ventilators and how they affect children pose additional problems. Children are so different, you need to stop and reassess actions you would normally take with an adult patient.

Program #6
What Matters in Respiratory Monitoring: What Goes and What Stays

Live Videoconference - August 22, 11:30 a.m.-1:00 p.m. Central Time
Teleconference with Videotape - September 26, 11:30 a.m.-12:00 Noon Central Time
Presenters: Dean R. Hess, PhD, RRT, FAARC and Richard D. Branson, BA, RRT

The health care provider has an array of monitoring devices available in managing a patient. With all that technology available, which device is appropriate? What about those displays on ventilators? The availability of graphics during mechanical ventilation can provide a wealth of information. When is it essential? Under what circumstances should you pay close attention to those displays in the assessment of your patient?

Program #7
Managing Asthma: An Update

Live Videoconference - September 19, 11:30 a.m.-1:00 p.m. Central Time
Teleconference with Videotape - October 17, 11:30 a.m.-12:00 Noon Central Time
Presenters: Patti Joyner, RRT, CCM and Mari Jones, MSN, RN, FNP, RRT

Asthma management is a hot topic for discussion. Everyone wants to implement a program at his or her facility. What will make a program work, and how do you know if it's successful? This program will provide you with the information you have been looking for in order to implement a program and determine how successful the program really is. You will be given guidance on how to analyze outcomes measures from a successful program.

Program #8
Routine Pulmonary Function Testing: Doing It Right

Live Videoconference - November 7, 11:30 a.m.-1:00 p.m. Central Time
Teleconference with Videotape - December 5, 11:30 a.m.-12:00 Noon Central Time
Presenters: Carl D. Mottram, BA, RRT, RPFT and David J. Pierson, MD, FAARC

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haled bronchodilators as first-line therapy. Anticholinergics are noted to be well tolerated, although potential problems with β_2-agonists are mentioned. The ERS and BTS suggest that inhaled corticosteroids may be of value in patients documented to be steroid responders, whereas the ATS does not recommend their use at all. All three guidelines support the use of oxygen and pulmonary rehabilitation. There are varying levels of disagreement between the guidelines related to the role of spirometry, stratification of disease severity, and the use of theophylline and systemic corticosteroids. Other differences include the role for nebulizers and metered-dose inhalers, secretion clearance methodologies, and the treatment of acute COPD exacerbations and acute respiratory failure. All three guidelines agree that more research is needed to improve our understanding and management of COPD.

Suboptimal Medical Therapy in COPD: Exploring the Causes and Consequences—Ramsey SD. Chest 2000 Feb;117(2 Suppl):33S-37S.

Effective outpatient management of COPD requires prescription of and adherence to appropriate therapies. Although practice guidelines for outpatient management of COPD are widely available, evidence suggests that these guidelines are not being implemented widely in clinical practice. Furthermore, several studies have shown that patient compliance with recommended therapy is poor. This paper discusses several reasons why implementation of practice guidelines and adherence with prescribed therapies may be poor. Potential clinical and economic consequences of suboptimal management are reviewed. Although the evidence suggests that improved compliance with guideline-recommended practice will improve symptoms and disease-specific quality of life, further work needs to be done to establish the cost-effectiveness of chronic therapies for COPD relative to other chronic conditions. Without such data, managed care organizations will be reluctant to allocate scarce resources toward expensive guideline implementation programs for individuals with this condition.

How Can the Implementation of Guidelines Be Improved?—Pearson MG. Chest 2000 Feb;117(2 Suppl):38S-41S.

Guidelines for a variety of diseases have now been produced. However, implementation of guidelines requires that the medical profession is willing to conform to patterns of diagnostic and treatment behavior set down by others. This may not happen in practice. Early experience in the United Kingdom was gained with the introduction of guidelines for the management of asthma. For a number of years, there have been improvements in practice, but deficiencies still exist. When the introduction of guidelines for the management of COPD was planned, a new approach was taken with a consortium of the British Thoracic Society, pharmaceutical companies, and medical equipment companies being formed to promote their use. Early studies show that COPD care starts from an even lower baseline than asthma; there is poor understanding of objective diagnosis of COPD in both primary and secondary care.

Assessment of Bronchodilator Efficacy in Symptomatic COPD: Is Spirometry Useful?—O'Donnell DE. Chest 2000 Feb;117(2 Suppl): 42S-47S.

Bronchodilator therapy in COPD is deemed successful if it improves ventilatory mechanics to a degree where effective symptom alleviation and increased exercise capacity are achieved. A greater understanding of the pathophysiologic mechanisms of dyspnea and exercise intolerance in COPD has prompted a reevaluation of the manner in which we currently assess therapeutic efficacy. The traditional reliance on an improved post-bronchodilator FEV_1 as indicative of a positive clinical response has recognized limitations. To the extent that pharmacologic volume reduction is a desirable therapeutic goal with favorable implications for dyspnea relief and increased exercise tolerance, the potential value of bronchodilator-induced changes in lung volume measurements is currently being studied. It is unlikely, however, given the multifactorial nature of dyspnea and exercise limitation in COPD, that resting spirometric measurements of maximal flows and volumes alone will be sufficiently sensitive to adequately predict a positive clinical response to bronchodilator therapy. Thus, additional direct measurements of exercise dynamic hyperinflation and exercise endurance together with reliable subjective measurements of dyspnea and quality of life are recommended in the setting of a suitable placebo-controlled design.

Impact of Sleep in COPD—McNicholas WT. Chest 2000 Feb;117(2 Suppl):48S-53S.

Sleep has well-recognized effects on breathing, including changes in central respiratory control, airways resistance, and muscular contractility, which do not have an adverse effect in healthy individuals but may cause problems in patients with COPD. Sleep-related hypoxemia and hypercapnia are well recognized in COPD and are most pronounced in rapid eye movement sleep. However, sleep studies are usually only indicated in patients with COPD when there is a possibility of sleep apnea or when cor pulmonale and/or polycythemia are not explained by the awake P_{aO_2} level. Management options for patients with sleep-related respiratory failure include general measures such as optimizing therapy of the underlying condition; physiotherapy and prompt treatment of infective exacerbations; supplemental oxygen; pharmacologic treatments such as bronchodilators, particularly ipratropium bromide, theophylline, and almitrine; and noninvasive positive pressure ventilation.

How Should Health-Related Quality of Life Be Assessed in Patients with COPD?—Mahler DA. Chest 2000 Feb;117(2 Suppl):54S-57S.

The traditional approach of caring for patients with chronic respiratory disease has been to rely on pulmonary function tests to quantify the severity and to assess response to therapy. However, patients with respiratory conditions seek medical attention because of symptoms, particularly dyspnea, and impaired ability to function, which clearly impact on an individual's health-related quality of life (HRQOL). Accordingly, instruments have been developed to provide a standardized method to measure health status and levels of impairment. One of the major reasons for measuring HRQOL is to detect how much HRQOL has changed in response to therapy (an evaluative instrument). A minimum clinically significant change has been established for some HRQOL instruments in order to indicate the relative value of any measured change and to guide the interpretation as to whether the change is "clinically meaningful." Selected studies using disease-specific instruments have demonstrated that β_2-agonist, anticholinergic, and theophylline medications can improve HRQOL, as compared with placebo therapy.

New Approaches to the Management of COPD—Stockley RA. Chest 2000 Feb;117(2 Suppl):58S-62S.

Airflow limitation in COPD is a result partially of bronchospasm, but it is also caused by a reduction in airway caliber, the number of small airways, airway collapse because of loss of connective tissue support, excess mucus in the airways, and edema of the airway wall. Structural changes also occur because of long-term destruction of interstitial connective tissue, including elastin. Therefore, in addition to the traditional aim of reversing bronchospasm with bronchodilators, disease-modifying approaches are being investigated. The enzyme neutrophil elastase is implicated in the induction of bronchial disease causing structural changes in lungs, impairment of mucociliary clearance, and impairment of host defenses. The precise mechanism pathway of neutrophil elastase is uncertain, but the effects of influencing the pathway in order to slow disease progression are being investigated. Oxidants may also have a role in the

development of COPD, with increased levels activating airway cells and cytokine production.

Obstructive Sleep Apnoea Syndrome As a Risk Factor for Hypertension: Population Study—Lavie P, Herer P, Hoffstein V. BMJ 2000 Feb 19;320(7233):479–482.

Objective: To assess whether sleep apnoea syndrome is an independent risk factor for hypertension. Design: Population study. Setting: Sleep clinic in Toronto. Participants: 2677 adults, aged 20–85 years, referred to the sleep clinic with suspected sleep apnoea syndrome. Outcome measures: Medical history, demographic data, morning and evening blood pressure, and whole night polysomnography. Results: Blood pressure and number of patients with hypertension increased linearly with severity of sleep apnoea, as shown by the apnoea-hypopnoea index. Multiple regression analysis of blood pressure levels of all patients not taking antihypertensives showed that apnoea was a significant predictor of both systolic and diastolic blood pressure after adjustment for age, body mass index, and sex. Multiple logistic regression showed that each additional apnoeic event per hour of sleep increased the odds of hypertension by about 1%, whereas each 10% decrease in nocturnal oxygen saturation increased the odds by 13%. Conclusion: Sleep apnoea syndrome is profoundly associated with hypertension independent of all relevant risk factors.

Partial Liquid Ventilation with Perflubron Attenuates in Vivo Oxidative Damage to Proteins and Lipids—Rotta AT, Gunnarsson B, Hernan LJ, Fuhrman BP, Steinhorn DM. Crit Care Med 2000 Jan;28(1): 202–208.

OBJECTIVE: To determine the impact of partial liquid ventilation on the degree of pulmonary damage by reactive oxygen species in a model of acute lung injury caused by systemic endotoxemia. DESIGN: A prospective, controlled, in vivo, animal laboratory study. SETTING: Animal research facility of a health sciences university. SUBJECTS: Forty New Zealand White rabbits. INTERVENTIONS: Mature rabbits were anesthetized and instrumented with a tracheostomy and vascular catheters. Animals were assigned to receive either partial liquid ventilation (n = 16) with perflubron (18 mL/kg via endotracheal tube) or conventional mechanical ventilation (n = 16). Both groups were ventilated using similar strategies, with an F_{IO_2} of 1.0 and tidal volume as required to obtain a normal P_{aCO_2}. Animals were then given 0.9 mg/kg *Escherichia coli* endotoxin intravenously over 30 mins. Eight uninjured instrumented and mechanically ventilated animals served as controls. Partial liquid ventilation or conventional ventilation was continued for 4 hrs before the animals were killed. Lung homogenates were analyzed for malondialdehyde (MDA) and 4-hydroxy-2(E)-nonenal (4-HNE) concentrations using a colorimetric assay. To assess protein oxidative damage, carbonyl groups in protein side chains were derivatized with 2,4-dinitrophenylhydrazine followed by Western blotting with a dinitrophenylated-specific primary antibody. MEASUREMENTS AND MAIN RESULTS: MDA (713.42±662 vs. 1601.4±1156 nmol/g protein; p = 0.023) and MDA plus 4-HNE (1480.24±788 vs. 2675.2±1628 nmol/g protein; p = 0.038) concentrations were lower in animals treated with partial liquid ventilation compared with conventionally ventilated animals, respectively. Animals treated with partial liquid ventilation exhibited attenuation of dinitrophenylated-derivatized protein bands by Western blotting, indicating a reduction in protein oxidative damage. The presence of perfluorocarbon did not interfere with the MDA assay when assessed by independent analysis in vitro. Perflubron did not serve as a sink for peroxyl radicals produced in the aqueous phase during separate in vitro oxidation experiments. CONCLUSIONS: Partial liquid ventilation attenuates oxidative damage to lipids and proteins during experimental acute lung injury. This finding is not caused by binding of lipid peroxidation products to perflubron or by the peroxyl radical scavenging properties of perflubron.

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Capillary Blood Gases in a Pediatric Intensive Care Unit—Escalante-Kanashiro R, Tantalean-Da-Fieno J. Crit Care Med 2000 Jan;28(1):224–226.

OBJECTIVE: To determine if samples obtained from arterial and capillary sources are comparable in children with diverse pathologic conditions during their stay in a pediatric intensive care unit. STUDY DESIGN: Prospective, descriptive study in patients admitted to a multidisciplinary pediatric intensive care unit. INTERVENTIONS: Seventy-five simultaneous paired samples (arterial and capillary) were obtained from patients with different degrees of capillary reperfusion, hemodynamic stability, blood pressure, and temperature. Both samples were analyzed ≤ 5 mins after collection. MEASUREMENTS AND MAIN RESULTS: The average correlations between arterial and capillary samples were 0.87 for pH, 0.86 for CO_2, and 0.65 for oxygen. Neither poor perfusion nor low temperature altered the correlation for pH or CO_2. The only condition that significantly affected the correlation was hypotension. CONCLUSION: Capillary blood sampling is a useful alternative to gasometric evaluation of critically ill children, even in the presence of hypothermia or hypoperfusion, provided that hypotension is not present.

Conventional Ventilation Versus High-Frequency Oscillation: Hemodynamic Effects in Newborn Babies—Simma B, Fritz M, Fink C, Hammerer I. Crit Care Med 2000 Jan;28(1):227–231.

OBJECTIVE: We conducted a prospective study to assess the hemodynamic effects of conventional mechanical ventilation (CMV) compared with high-frequency oscillation (HFO) in newborn babies with respiratory distress syndrome. METHODS: A total of 18 consecutive term and preterm infants were examined by two-dimensional M-mode and pulsed Doppler echocardiography. RESULTS: Five patients had to be excluded, three of them because of increasing cardiovascular support after initiation of HFO. The remaining 13 infants (seven males, six females) had a

median gestational age of 33 wks (range, 25–40) and a birth weight of 2350 g (range, 790-3600). Patients entered the study at 21 hrs (range, 5–69) of life, receiving total maintenance fluid of 90 mL/kg/day (range, 60–120). Five babies (38%) needed continuous inotropic support. HFO was used as a rescue therapy in infants who failed with CMV. In all 13 patients, HFO significantly impaired cardiac performance compared with CMV by decreasing aortic velocity-time integral: median, 10.2 cm (range, 6.0–14.6) vs. 8.3 cm (range, 5.3–12.4; $p<0.002$); stroke volume: median, 3.8 mL (range, 1.6–6.8) vs. 3.2 mL (range, 1.3–5.9; $p<0.002$); and cardiac index: 281 mL/min/kg of body weight (range, 177–579) vs. 200 mL/min/kg of body weight (range, 156–591; $p<0.002$). Fractional shortening was also significantly reduced: median, 0.31% (range, 0.24–0.44) vs. 0.29% (range, 0.20–0.34; $p<0.01$), because of a significantly smaller left ventricular diastolic diameter during HFO: median, 1.4 cm (range, 1.0–1.9) vs. 1.4 cm (range, 0.9–1.8; $p<0.05$), with a median difference of -0.07 cm (range, -0.4–0.2). HFO also causes a significant decrease in heart rate-corrected left ventricular ejection time: median, 0.25 sec (range, 0.23–0.28) vs. 0.23 sec (range, 0.21–0.26; $p < 0.02$) and heart rate-corrected velocity of circumferential fiber shortening (Vcfc): median, 1.3 circ/sec (range, 1.0–1.6) vs. 1.2 circ/sec (range, 0.9–1.4; $p<.05$). Left ventricular end-systolic wall stress (LVESWS; g/cm^2) remained stable. The correlation between Vcfc and LVESWS did not show any significance (CMV, $r^2 = 0.2$; HFO, $r^2 = 0.09$). The regression line between Vcfc and LVESWS showed a higher y-intercept and steeper slope during CMV than during HFO. Heart rate, mean arterial pressure, and left ventricular systolic diameter remained unchanged. CONCLUSIONS: In newborn babies, HFO significantly decreased left ventricular cardiac output caused by reduced left ventricular filling and HFO decreased contractility at higher mean airway pressures than with CMV.

Consensus Conference Definitions for Sepsis, Septic Shock, Acute Lung Injury, and Acute Respiratory Distress Syndrome: Time for a Reevaluation (consensus development conference review)—Abraham E, Matthay MA, Dinarello CA, Vincent JL, Cohen J, Opal SM, et al. Crit Care Med 2000 Jan;28(1):232–235.

Definitions for sepsis, septic shock, acute lung injury (ALI), and acute respiratory distress syndrome (ARDS) were developed by consensus conferences with the goal of achieving standardization of terminology and improved homogeneity of patient populations in clinical studies. Although such definitions have been useful in epidemiologic investigations, the criteria specified by the consensus conferences are broad and insufficiently specific to address the problem of heterogeneous mechanisms leading to clinical syndromes. An important challenge is to progress from clinical syndromes, as presently defined, to more specific entities that are delineated by alterations in specific immunologic or biochemical pathways. Such mechanistic definitions will provide more homogeneous groups of patients who can be identified at early stages of their clinical course. This approach encourages focused investigation of pathways leading to organ system dysfunction and death and, also, provides an efficient framework for the development of new therapies useful in critically ill patients.

Survivors of Catastrophic Illness: Outcome after Direct Transfer from Intensive Care to Extended Care Facilities—Nasraway SA, Button GJ, Rand WM, Hudson-Jinks T, Gustafson M. Crit Care Med 2000 Jan;28(1):19–25.

OBJECTIVE: To describe outcomes of adult survivors of prolonged critical illness after direct transfer to extended care facilities. DESIGN: A retrospective cohort study. SETTING: All adult intensive care units (ICUs) in a tertiary care university hospital. PATIENTS: A consecutive series of 97 adult survivors with an ICU stay of $\geq$ 7 days transferred directly from intensive care to extended care facilities between 1990 and 1996. INTERVENTIONS: None. METHODS AND MAIN RESULTS: Hospital and extended care facility charts were reviewed for patient characteristics, resource utilization, and survival. Survivors were for a minimum of 1 yr and a maximum of 6 yrs, and were interviewed to assess quality of life and functionality. The mean age of the patients was 66±16 (range, 19–93) yrs. The median length of ICU stay for these patients was 39 (range, 7–276) days. Only 18 of the 71 ventilator-assisted patients were weaned from mechanical ventilation after transfer to the extended care facility. Survival for the study period, at 1 yr after discharge from the ICU, was 49.5%. One year after discharge from the ICU, 11.5% of all patients had returned home, were breathing spontaneously, had a fair or better quality of life, and had good physical functionality. Each successive year, an increasing proportion of patients underwent direct transfer to an extended care facility. This strategy decreased the patients' length of stay ($p<0.002$) in the ICU from year to year, but was significantly associated with an increase in readmissions to acute care hospitals ($p<0.002$). CONCLUSIONS: Survivors of catastrophic illness who are so debilitated that they require transfer to an extended care facility have a low likelihood of achieving both survival and functional independence 1 yr after discharge from the ICU. Aggressive cost-conscious strategies to accelerate the transfer of these patients successfully reduced the length of ICU stay and hospital costs, but were associated with a high rate of readmission to tertiary care facilities.

Accidental Removal of Endotracheal and Nasogastric Tubes and Intravascular Catheters—Carrion MI, Ayuso D, Marcos M, Paz Robles M, de la Cal MA, Alia I, Esteban A. Crit Care Med 2000 Jan;28(1):63–66.

OBJECTIVES: To characterize the rates of accidental removal of endotracheal tubes, nasogastric tubes, central venous catheters, and arterial catheters. To assess the efficacy of corrective measures aimed at reducing the accidental removal of these devices. DESIGN: Prospective, observational, and interventional study. SETTING: Eighteen-bed medical-surgical intensive care unit of a 650-bed tertiary care hospital. PATIENTS: Patients admitted to the intensive care unit who had any of the following devices in place for more than 24 hrs: endotracheal tube, nasogastric tube, central venous catheter, arterial catheter. MEASUREMENTS AND INTERVENTIONS: Data were collected on the date of placement of tubes and catheters, position of vascular catheters, date of removal, and reason for removal. The study involved three consecutive 6-month periods. At the end of the first and the second periods, information about rates of accidental removal was provided to the physicians and nurses. In addition, the personnel were instructed to be more vigilant and specific measures aimed at reducing the accidental removal were introduced. MAIN RESULTS: In the first period, 289 endotracheal tubes were placed and 13.1% (24.7 per 1000 days) were removed accidentally. In the second and third periods, 17.1% (25.5 per 1000 days) and 11.4% (15.1 per 1000 days) were removed accidentally, respectively. In the first period, 368 nasogastric tubes were placed and 41% (73.9 per 1000 days) were removed accidentally. In both the second and the third period, a significant reduction in the rate of accidental removal was observed (32.4% or 41.2 per 1000 days and 25.8% or 29.8 per 1000 days, respectively). A significant decrease was observed in the rates of accidental removal of central venous catheters from 7.5% (12.4 per 1000 days) in the first period to 3.6% (5.4 per 1000 days) in the second period. The rate of arterial catheters accidentally removed expressed according to the time at risk significantly decreased from 46.5 per 1000 days in the first period to 19.1 per 1000 days in the second period and 25.3 per 1000 days in the third period. CONCLUSIONS: The information provided by the rates of accidental removal expressed by patient-days is helpful to compare results obtained in populations with different times of follow-up. Education of medical personnel and limiting upper-extremity access to within 20 cm from any catheter or tube resulted in a significant reduction of patient-related removal of tubes and catheters.

Interhospital Transport of the Extremely Ill Patient: The Mobile Intensive Care Unit—Gebremichael M, Borg U, Habashi NM, Cotting-

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ham C, Cunsolo L, McCunn M, Reynolds HN. Crit Care Med 2000 Jan;28(1):79–85.

BACKGROUND: Critically ill patients may require specialized care that is offered only at tertiary referral centers. As regionalization and specialization of critical care become more common, transportation of critically ill patients must be refined. Transportation of critically ill patients within a hospital, much less outside the hospital, is often deemed unsafe because of medical instability. We report, here, our results from 2 yrs' experience of transporting extremely ill patients with respiratory failure via a ground critical care transport service. METHODS: A mobile intensive care unit was equipped and staffed to nearly recreate the intensive care environment. Staffing included a physician, nurse, respiratory therapist, and driver–all with extensive critical care experience. The mobile intensive care unit was equipped with a full pharmacy, advanced ventilatory equipment, and capability for full invasive hemodynamic monitoring. Data were analyzed by retrospective review. The predicted mortality rate, based on P_{aO_2}/F_{IO_2} ratios, was compared with the actual mortality rate. RESULTS: During a 2-yr period, 39 critically ill patients were transported. Thirty-six of the 39 were candidates for extracorporeal lung assist, with a mean positive end-expiratory pressure requirement of 15.9, a mean F_{IO_2} requirement of 0.93, and a mean P_{aO_2}/F_{IO_2} ratio of 59.8. Pulmonary arterial catheters and peripheral arterial catheters were in place in 66.6% and 72% of patients, respectively. Vasoactive medications were being infused in 56%, and 74% were receiving medical paralytics. One patient died during movement from the bed to the transport gurney. Other than one episode of transient hypotension, there were no complications or untoward outcomes related to transport. Unique therapeutic interventions were performed at the receiving facility on 34 of 39 patients. The predicted mortality rate, based on indicators of lung dysfunction, was 68% to 100%; the actual subsequent hospital mortality rate was 43%. CONCLUSIONS: When a mobile intensive care unit is properly staffed and equipped and patient stabilization is performed before transfer, severely ill patients with respiratory failure can be transferred safely. For patients with respiratory failure, there may be a survival advantage in transfer to regional centers of expertise.

Complications of Prone Ventilation in Patients with Multisystem Trauma with Fulminant Acute Respiratory Distress Syndrome—Offner PJ, Haenel JB, Moore EE, Biffl WL, Franciose RJ, Burch JM. J Trauma 2000 Feb;48(2):224–228.

INTRODUCTION: Prone ventilation improves oxygenation in selected patients with acute respiratory distress syndrome (ARDS). However, prone positioning of critically ill patients with multiple invasive lines and tubes is potentially dangerous. Trauma patients, in particular, may require special consideration because of skeletal fixation devices or prior operative procedures. Our objective was to critically evaluate our experience with prone positioning in patients with severe postinjury ARDS. METHODS: Injured patients admitted to our Level I trauma center who developed ARDS were prospectively identified. Serial lung injury severity and pulmonary mechanical data, as well as complications of prone ventilation were recorded. RESULTS: During the 12-month period ending August of 1998, nine patients with postinjury ARDS were treated with prone ventilation because of hypoxemia refractory to other ventilatory strategies. All patients suffered blunt trauma. Their mean age was 29 $\pm$ 4.5 years; seven patients were men. The average Injury Severity Score was 26 $\pm$ 5; and, at the time of prone positioning, the mean Lung Injury Score was 3.5. The mean P_{aO_2}/F_{IO_2} ratio increased from 75 $\pm$ 7 to 147 $\pm$ 27 with prone ventilation ($p < 0.05$, paired t test); and in six patients, the F_{IO_2} could be decreased. Four major complications occurred (44%). One patient experienced a midline abdominal wound dehiscence. Severe facial or upper chest wall pressure necrosis developed in two patients, despite extensive padding and careful attention to skin care. The fourth patient sustained a cardiac arrest immediately after prone positioning. CONCLUSION: Prone ventilation in postinjury patients with ARDS may improve oxygenation but has the potential for significant complications. Careful consideration is required before prone positioning in this subset of patients.

Outcomes of Trauma Patients Who Survive Prolonged Lengths of Stay in the Intensive Care Unit—Miller RS, Patton M, Graham RM, Hollins D. J Trauma 2000 Feb;48(2):229–234.

OBJECTIVE: To examine a subgroup of severely injured patients spending $\geq$ 3 weeks in the intensive care unit (ICU) and to determine their disposition and eventual functional outcome. METHODS: A retrospective review of our trauma registry and medical records over a 7-year period (January of 1991 to December of 1997) identified 115 patients with ICU length of stay (LOS) $\geq$ 3 weeks. Variables selected included age, length of stay, injury severity score, injuries, disposition, and charges. Functional independence measures (FIM) were obtained in patients requiring inpatient rehabilitation and a written questionnaire (Rand 36-item Health Survey) was mailed to all patients alive at discharge. RESULTS: Mean ICU length of stay of the 115 patients was 36 days (range, 21–106 days); mean age, 49 years (range, 4–89 years); 73 patients (63%) were males, 42 patients (37%) were females. Overall mortality was 22% (n = 25). The remaining 90 patients survived to discharge with the following disposition: rehabilitation facility 60% (n = 54), home with temporary disability 22% (n = 20), nursing home 8% (n = 7), home with permanent disability 4% (n = 4), transferred 6% (n = 5). Mean hospital charge was $193,000 (range, $77,000-$528,000). No variable or combination could predict outcome except age. Elderly patients (age $\geq$ 75, n = 24) had an overall mortality of 42% (n = 10). Eight of 14 survivors fulfilled admission criteria and entered our rehabilitation facility. The remaining six elderly patients either went to nursing homes or were permanently disabled. Complete FIM scores were available on 47 of 54 patients who went to rehabilitation facility. The mean rehabilitation facility admission FIM score was 52, indicating either complete dependence or the need for moderate assistance. After they had remained at the rehabilitation facility for a mean of 48 days (range, 7–278 days), patients' FIM scores improved to a mean of 86, signifying minimal contact assistance or supervision only. Three-month follow-up FIM scores continued to improve to a mean of 101, a score denoting complete independence. Elderly patients within the rehabilitation facility fared as well as the younger group. For the Rand-36 survey, 47 of 90 patients or family members were contacted. Twelve patients died since discharge, leaving 35 patients to complete the survey. Despite excellent FIM scores, overall mean health was only fair to good, with limitations to activity and lack of energy cited as the main problems. CONCLUSION: Despite tremendous resource utilization, the majority of trauma patients with prolonged ICU stays can eventually return to varying degrees of functional daily living and independence, but not to preinjury levels. A subgroup of severely injured elderly patients had a significantly higher mortality rate. However, elderly survivors that entered our rehabilitation facility fared as well as the younger patients.

Domestic Violence in a University Emergency Department—Ernst AA, Weiss SJ, Nick TG, Casalletto J, Garza A. South Med J 2000 Feb;93(2):176–181.

BACKGROUND: We attempted to determine the prevalence and demographics of domestic violence (DV) among male and female patients in a university emergency department (ED). METHODS: The validated Index of Spouse Abuse (ISA) was used. Patients aged 18 years or older seen during 28 randomly selected 4-hour shifts were eligible. RESULTS: Of the 97 participants in the study, 57 were female. One man and 3 women were victims of present physical DV, with 1 male and 2 female victims of present nonphysical abuse. Three of the 40 men and 22 of the 57 women had been victims of past physical violence. One man and 15 women had been victims of past nonphysical abuse. Alcohol use, suicidal

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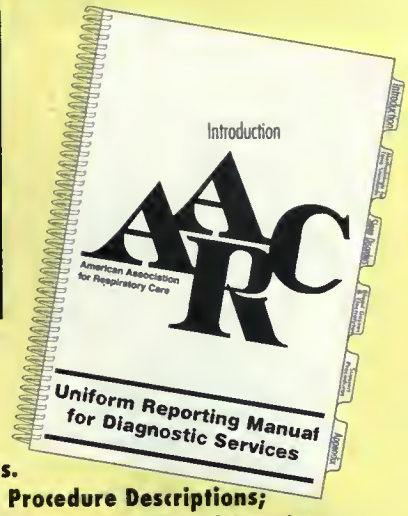

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ideation, family history, and psychiatric history were all strongly correlated with DV. CONCLUSIONS: The prevalence of DV past was significantly higher in the females. Present violence was more rare and less than that reported in other ED studies.

Accuracy of Clinical Evaluation in the Determination of Brain Death—Flowers WM Jr, Patel BR. South Med J 2000 Feb;93(2):203–206.

BACKGROUND: The accuracy of the clinical diagnosis of brain death has never been established. METHODS: Seventy-one consecutive clinically brain dead patients were studied retrospectively. Inclusion criteria were complete cessation of brain function with profound coma of known cause, complete absence of brain stem reflexes, and apnea, all persisting for a least 6 hours. A formal apnea test with a documented P_{CO_2} of $>$ 60 mm Hg was required. All evaluations were done by experienced neurosurgery or neurology resident or staff physicians. The clinical diagnosis was compared with the results of radionuclide angiography and with the clinical course and final outcome. RESULTS: Seventy patients had no arterial blood flow on radionuclide angiography. One blood flow study was considered to have yielded a false-negative result. No patient recovered or survived. CONCLUSIONS: The clinical diagnosis of brain death is highly reliable when made by experienced examiners using established criteria. In this study, the accuracy was 100%.

Supplemental Therapeutic Oxygen for Prethreshold Retinopathy Of Prematurity (STOP-ROP): A Randomized, Controlled Trial. I: Primary Outcomes. Pediatrics 2000 Feb;105(2):295–310.

OBJECTIVE: To determine the efficacy and safety of supplemental therapeutic oxygen for infants with prethreshold retinopathy of prematurity (ROP) to reduce the probability of progression to threshold ROP and the need for peripheral retinal ablation. METHODS: Premature infants with confirmed prethreshold ROP in at least 1 eye and median pulse oximetry <94% saturation were randomized to a conventional oxygen arm with pulse oximetry targeted at 89% to 94% saturation or a supplemental arm with pulse oximetry targeted at 96% to 99% saturation, for at least 2 weeks, and until both eyes were at study endpoints. Certified examiners masked to treatment assignment conducted weekly eye examinations until each study eye reached ophthalmic endpoint. An adverse ophthalmic endpoint for an infant was defined as reaching threshold criteria for laser or cryotherapy in at least 1 study eye. A favorable ophthalmic endpoint was regression of the ROP into zone III for at least 2 consecutive weekly examinations or full retinal vascularization. At 3 months after the due date of the infant, ophthalmic findings, pulmonary status, growth, and interim illnesses were again recorded. RESULTS: Six hundred forty-nine infants (325 conventional and 324 supplemental) were enrolled from 30 centers over 5 years. Five hundred ninety-seven (92.0%) infants attained known ophthalmic endpoints, and 600 (92%) completed the ophthalmic 3-month assessment. The rate of progression to threshold in at least 1 eye was 48% in the conventional arm and 41% in the supplemental arm. After adjustment for baseline ROP severity stratum, plus disease, race, and gestational age, the odds ratio (supplemental vs conventional) for progression was 0.72 (95% confidence interval: 0.52, 1.01). Final structural status of all study eyes at 3 months of corrected age showed similar rates of severe sequelae in both treatment arms: retinal detachments or folds (4.4% conventional vs 4.1% supplemental), and macular ectopia (3.9% conventional vs 3.9% supplemental). Within the prespecified ROP severity strata, ROP progression rates were lower with supplemental oxygen than with conventional oxygen, but the differences were not statistically significant. A post hoc subgroup analysis of plus disease (dilated and tortuous vessels in at least 2 quadrants of the posterior pole) suggested that infants without plus disease may be more responsive to supplemental therapy (46% progression in the conventional arm vs 32% in the supplemental arm) than infants with plus disease (52% progression in conventional vs 57% in supplemental). Pneumonia and/or exacerbations of chronic lung disease occurred in more infants in the supplemental arm (8.5% conventional vs 13.2% supplemental). Also, at 50 weeks of postmenstrual age, fewer conventional than supplemental infants remained hospitalized (6.8% vs 12.7%), on oxygen (37.0% vs 46.8%), and on diuretics (24.4% vs 35. 8%). Growth and developmental milestones did not differ between the 2 arms. CONCLUSIONS: Use of supplemental oxygen at pulse oximetry saturations of 96% to 99% did not cause additional progression of prethreshold ROP but also did not significantly reduce the number of infants requiring peripheral ablative surgery. A subgroup analysis suggested a benefit of supplemental oxygen among infants who have prethreshold ROP without plus disease, but this finding requires additional study. Supplemental oxygen increased the risk of adverse pulmonary events including pneumonia and/or exacerbations of chronic lung disease and the need for oxygen, diuretics, and hospitalization at 3 months of corrected age. Although the relative risk/benefit of supplemental oxygen for each infant must be individually considered, clinicians need no longer be concerned that supplemental oxygen, as used in this study, will exacerbate active prethreshold ROP.

Can Peak Expiratory Flow Predict Airflow Obstruction in Children with Asthma?—Eid N, Yandell B, Howell L, Eddy M, Sheikh S. Pediatrics 2000 Feb;105(2):354–358.

STUDY OBJECTIVES. A recent trend in the treatment of asthma has been the widespread, independent use of peak expiratory flow (PEF). We examined whether PEF monitoring creates inaccuracies in assessment of children with moderate to severe asthma. METHODS. We compared the negative predictive value of PEF in relation to the forced expiratory volume in 1 second (FEV_1), and to the forced expiratory flow between 25% and 75% of the vital capacity ($FEF_{25-75\%}$) at different levels of air trapping as determined by the residual volume over total lung capacity ratio (RV/TLC). RESULTS. The study included 244 patients, ages 4 to 18 years with all classes of asthma severity, with FEV_1 ranging from 28% to 134% of predicted value. We analyzed 367 sets of pulmonary function tests performed throughout a 3-year period. Thirty percent of patients with a normal PEF value had an abnormal FEV_1 or $FEF_{25-75\%}$. As air trapping increased, the ability of a normal PEF to predict normal FEV_1 and $FEF_{25-75\%}$ readings fell from 83% to 53%. The negative predictive value was significantly lower for patients with RV/TLC ratio >30 compared with patients with RV/TLC <30. CONCLUSIONS. The results of this study suggest that it might be possible to identify children for whom the PEF is likely to give false-negative results. As air trapping increases, it causes the PEF to give misleading reassurance of normal pulmonary function. Furthermore, poor predictiveness of PEF is obtained when values 80% of predicted for age are considered normal.

Nocturnal Pulse Oximetry As an Abbreviated Testing Modality for Pediatric Obstructive Sleep Apnea—Brouillette RT, Morielli A, Leimanis A, Waters KA, Luciano R, Ducharme FM. Pediatrics 2000 Feb; 105(2):405–412.

OBJECTIVE. To determine the utility of pulse oximetry for diagnosis of obstructive sleep apnea (OSA) in children. METHODS. We performed a cross-sectional study of 349 patients referred to a pediatric sleep laboratory for possible OSA. A mixed/obstructive apnea/hypopnea index (MOAHI) greater than or equal to 1 on nocturnal polysomnography (PSG) defined OSA. A sleep laboratory physician read nocturnal oximetry trend and event graphs, blinded to clinical and polysomnographic results. Likelihood ratios were used to determine the change in probability of having OSA before and after oximetry results were known. RESULTS. Of 349 patients, 210 (60%) had OSA as defined polysomnographically. Oximetry trend graphs were classified as positive for OSA in 93 and negative or inconclusive in 256 patients. Of the 93 oximetry results read as positive, PSG confirmed OSA in 90 patients. A positive oximetry trend graph had a likelihood ratio of 19.4, increasing the prob-

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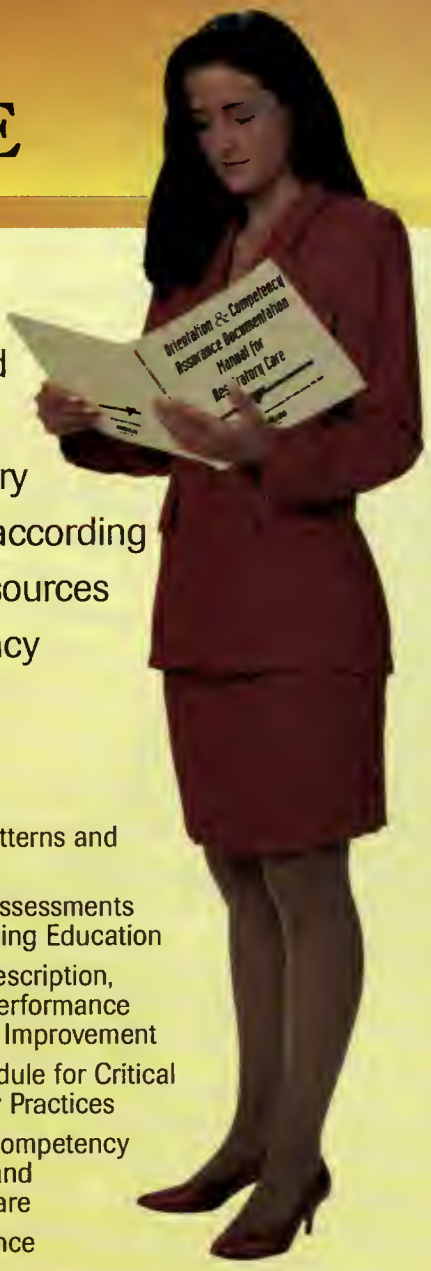

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ability of having OSA from 60% to 97%. The median MOAHI of children with a positive oximetry result was 16.4 (7.5, 30.2). The 3 false-positive oximetry results were all in the subgroup of 92 children who had diagnoses other than adenotonsillar hypertrophy that might have affected breathing during sleep. A negative or inconclusive oximetry result had a likelihood ratio of 0.58, decreasing the probability of having OSA from 60% to 47%. Interobserver reliability for oximetry readings was very good to excellent (kappa = 0.80). CONCLUSIONS. In the setting of a child suspected of having OSA, a positive nocturnal oximetry trend graph has at least a 97% positive predictive value. Oximetry could: 1) be the definitive diagnostic test for straightforward OSA attributable to adenotonsillar hypertrophy in children older than 12 months of age, or 2) quickly and inexpensively identify children with a history suggesting sleep-disordered breathing who would require PSG to elucidate the type and severity. A negative oximetry result cannot be used to rule out OSA.

Low-Dose Nitric Oxide Therapy for Persistent Pulmonary Hypertension of the Newborn. Clinical Inhaled Nitric Oxide Research Group—Clark RH, Kueser TJ, Walker MW, Southgate WM, Huckaby JL, Perez JA,et al. N Engl J Med 2000 Feb 17;342(7):469–474.

BACKGROUND: Inhaled nitric oxide improves gas exchange in neonates, but the efficacy of low-dose inhaled nitric oxide in reducing the need for extracorporeal membrane oxygenation has not been established. METHODS: We conducted a clinical trial to determine whether low-dose inhaled nitric oxide would reduce the use of extracorporeal membrane oxygenation in neonates with pulmonary hypertension who were born after 34 weeks' gestation, were 4 days old or younger, required assisted ventilation, and had hypoxemic respiratory failure as defined by an oxygenation index of 25 or higher. The neonates who received nitric oxide were treated with 20 ppm for a maximum of 24 hours, followed by 5 ppm for no more than 96 hours. The primary end point of the study was the use of extracorporeal membrane oxygenation. RESULTS: Of 248 neonates enrolled, 126 were randomly assigned to the nitric oxide group and 122 to the control group. Extracorporeal membrane oxygenation was used in 78 neonates in the control group (64 percent) and in 48 neonates in the nitric oxide group (38 percent) ($p=0.001$). The 30-day mortality rate in the two groups was similar (8 percent in the control group and 7 percent in the nitric oxide group). Chronic lung disease developed less often in neonates treated with nitric oxide than in those in the control group (7 percent vs. 20 percent, $p=0.02$). The efficacy of nitric oxide was independent of the base-line oxygenation index and the primary pulmonary diagnosis. CONCLUSIONS: Inhaled nitric oxide reduces the extent to which extracorporeal membrane oxygenation is needed in neonates with hypoxemic respiratory failure and pulmonary hypertension.

Positive End-Expiratory Pressure Improves Respiratory Function in Obese but Not in Normal Subjects During Anesthesia and Paralysis—Pelosi P, Ravagnan I, Giurati G, Panigada M, Bottino N, Tredici S, et al. Anesthesiology 1999 Nov;91(5):1221–1231.

BACKGROUND: Morbidly obese patients, during anesthesia and paralysis, experience more severe impairment of respiratory mechanics and gas exchange than normal subjects. The authors hypothesized that positive end-expiratory pressure (PEEP) induces different responses in normal subjects ($n = 9$; body mass index < 25 kg/m^2) versus obese patients ($n = 9$; body mass index > 40 kg/m^2). METHODS: The authors measured lung volumes (helium technique), the elastances of the respiratory system, lung, and chest wall, the pressure-volume curves (occlusion technique and esophageal balloon), and the intraabdominal pressure (intrabladder catheter) at PEEP 0 and 10 cm H_2O in paralyzed, anesthetized postoperative patients in the intensive care unit or operating room after abdominal surgery. RESULTS: At PEEP 0 cm H_2O, obese patients had lower lung volume (0.59 ± 0.17 vs. 2.15 ± 0.58 l [mean $\pm$ SD], $p < 0.01$); higher elastances of the respiratory system (26.8 ± 4.2 vs. 16.4 ± 3.6 cm H_2O/L, $p < 0.01$), lung (17.4 ± 4.5 vs. 10.3 ± 3.2 cm H_2O/L, $p < 0.01$), and chest wall (9.4 ± 3.0 vs. 6.1 ± 1.4 cm H_2O/L, $p < 0.01$); and higher intraabdominal pressure (18.8 ± 7.8 vs. 9.0 ± 2.4 cm H_2O, $p < 0.01$) than normal subjects. The arterial oxygen tension was significantly lower (110 ± 30 vs. 218 ± 47 mm Hg, $p < 0.01$; inspired oxygen fraction = 50%), and the arterial carbon dioxide tension significantly higher (37.8 ± 6.8 vs. 28.4 ± 3.1, $p < 0.01$) in obese patients compared with normal subjects. Increasing PEEP to 10 cm H_2O significantly reduced elastances of the respiratory system, lung, and chest wall in obese patients but not in normal subjects. The pressure-volume curves were shifted upward and to the left in obese patients but were unchanged in normal subjects. The oxygenation increased with PEEP in obese patients (from 110 ± 30 to 130 ± 28 mmHg, $p < 0.01$) but was unchanged in normal subjects. The oxygenation changes were significantly correlated with alveolar recruitment ($r = 0.81$, $p < 0.01$). CONCLUSIONS: During anesthesia and paralysis, PEEP improves respiratory function in morbidly obese patients but not in normal subjects.

Supplemental Oxygen Reduces the Incidence of Postoperative Nausea and Vomiting—Greif R, Laciny S, Rapf B, Hickle RS, Sessler DI. Anesthesiology 1999 Nov;91(5):1246–1252.

BACKGROUND: Despite new anesthetic drugs and antiemetics, particularly 5-hydroxytrypta-mines, the incidence of postoperative nausea or vomiting remains between 20% and 70%. The authors tested the hypothesis that supplemental perioperative oxygen administration reduces the incidence of postoperative nausea or vomiting. METHODS: Patients undergoing colon resection were anesthetized with fentanyl and isoflurane. During and for 2 h after surgery they were randomly assigned to (1) 30% oxygen, balance nitrogen ($n = 119$); or (2) 80% oxygen, balance nitrogen ($n = 112$). The incidence of nausea or vomiting during the first 24 postoperative hours was evaluated by nurses blinded to group assignment and oxygen concentration. Data were analyzed with unpaired t or Mann-Whitney U tests. Results are presented as means $\pm$ SD; $p < 0.05$ was considered significant. RESULTS: Factors known to influence nausea and vomiting were comparable in the two groups. Perioperative oxygen saturation was well within normal limits in each treatment group; saturations the first postoperative morning were comparable in each group. Supplemental oxygen reduced the incidence of postoperative nausea or vomiting from 30% in the patients given 30% oxygen to 17% in those given 80% oxygen ($p = 0.027$). CONCLUSIONS: Supplemental oxygen reduced the incidence of postoperative nausea or vomiting nearly twofold after colorectal surgery. The mechanism by which oxygen administration reduces the incidence of these postoperative sequelae remains unknown but may be related to subtle intestinal ischemia. Because oxygen is inexpensive and essentially risk-free, supplemental oxygen appears to be an effective method of reducing postoperative nausea and vomiting.

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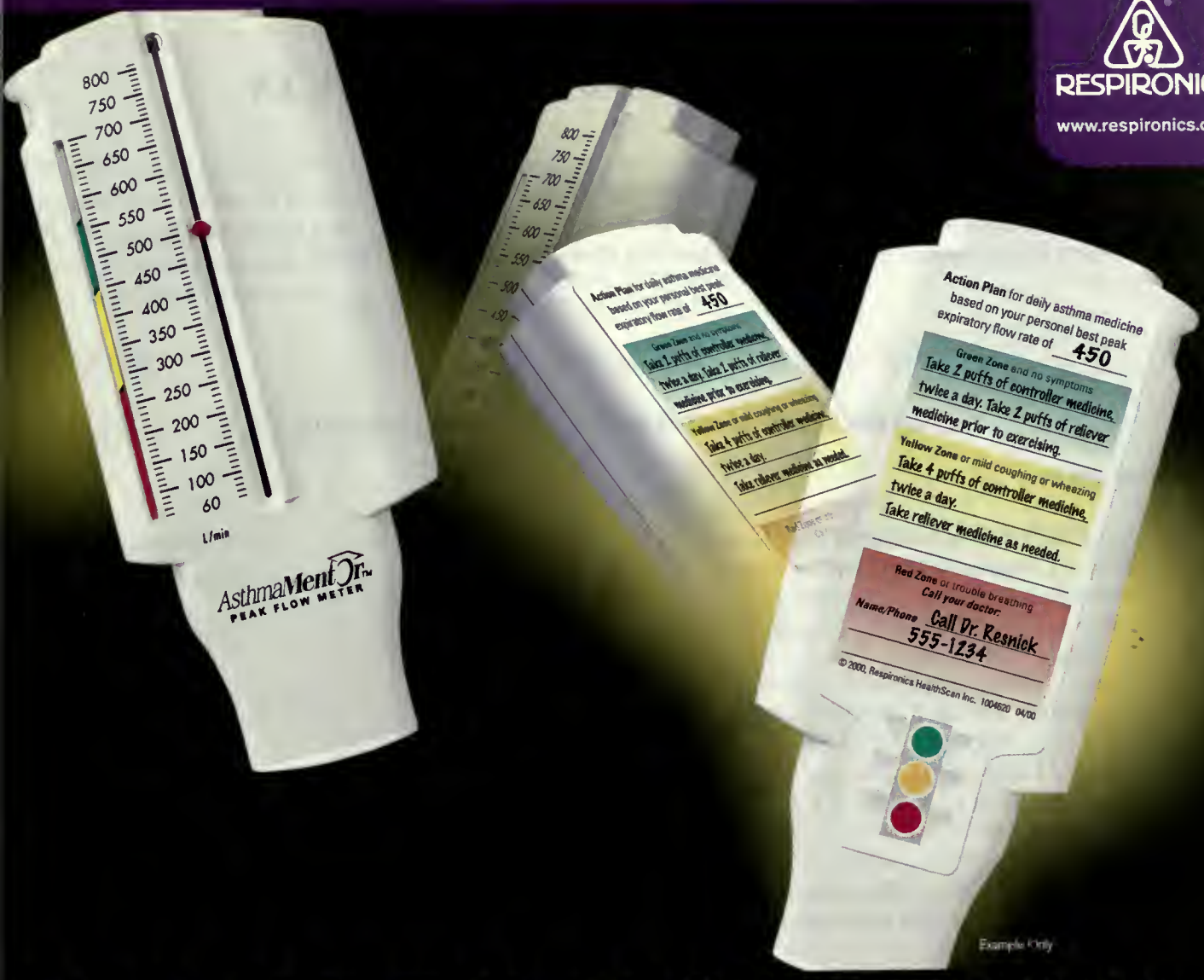

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Consensus Conference on Aerosols and Delivery Devices: Foreword

This issue of RESPIRATORY CARE contains the proceedings of a consensus conference on aerosols and delivery devices, convened last fall on behalf of the American Association for Respiratory Care (AARC) and the Journal by the American Respiratory Care Foundation (ARCF). This marks the fifth consensus conference to be published in the Journal since 1991, and the second to deal with aerosol therapy.

At the beginning of the last decade there was increasing national concern for health care costs in the face of burgeoning technology in both diagnosis and therapy. In addition, as the 1990s began, the AARC was embarking on an ambitious program to create clinical practice guidelines in respiratory care. In view of the central role of aerosols in all aspects of practice, administration, and research in respiratory care, the time was right for a consensus conference on aerosol delivery. Accordingly, the ARCF convened a group of acknowledged experts in January 1991 to discuss the most important aspects of aerosol delivery and to develop consensus recommendations.

This group's consensus document, plus state-of-the-art review papers on the individual topics discussed at the conference, were published in the September 1991 issue of RESPIRATORY CARE. It quickly became clear that the decision to hold the conference and disseminate the information it generated had been a good one. That issue, long out of print, has been the most requested individual issue the Journal has ever published. The consensus document was reprinted in *Chest*.[1] Subsequently referred to many times both in research papers and in chapters and reviews, it has more often been cited in its *Chest* version than in its parent journal since the latter was not at that time included in *Index Medicus*.

Was a second consensus conference needed on aerosols and aerosol delivery? I think there can be little doubt that it was. Few areas of medicine have evolved so rapidly. Changes in the management of pulmonary infections with *Pneumocystis carinii* and respiratory syncytial virus have shifted attention to other fronts. Global reduction of atmospheric chlorofluorocarbons is now a reality, and with it have come new propellants and delivery devices for aerosolized drugs. The drugs themselves have continued to evolve, both in traditional categories such as beta-agonist bronchodilators and corticosteroids and in new areas such as hormones, enzymes, surface active materials, and soon even gene therapy. Advances in the modeling and measurement of aerosol behavior and effects have been impressive. It was also important to revisit cost and regulatory issues related to aerosols and delivery devices.

The topic of this conference is important to industry, an arena in which change since the first consensus conference has been at least as dramatic as it has been on the scientific and clinical fronts. Thirteen companies involved in aerosols and aerosol delivery participated in the 1991 consensus conference as either sponsors or donors. Of that number, only 4 were at the table in 1999. Some of the others are no longer in business, and some of the companies participating this year did not exist in 1991, at least in their present forms.

The 1999 conference was convened and conducted much like its predecessor. A planning committee identified the most important topics to discuss and the most appropriate individuals to be invited to address them. As before, the committee also invited several others in the field, designated special advisors, whose contributions they felt would be important in developing the consensus document. The ARCF agreed to host the conference and to solicit funds from industry to pay for it. Each industry sponsor designated a respondent to participate in the discussions. Other representatives from research, clinical practice, and industry were present but did not participate. As in 1991, Neil MacIntyre introduced and moderated the discussions; he and Myrna Dolovich steered the consensus document through the revision process and served as guest editors for the issue.

During the conference, formal presentation of a review of each topic was followed by general discussion. After completion of the individual presentations, the writing committee met on site to prepare a working draft of the consensus document, which was then presented to the whole group. More discussion followed, with modifications both at the conference and in several subsequent mailings to the faculty and special advisors. The final consensus document was circulated for comment to all participants.

Like those of its predecessor, the proceedings of this consensus conference on aerosols and delivery devices are intended to inform and assist the clinicians, investigators, manufacturers, regulators, and others who participate in this important area of respiratory care.

David J Pierson MD FAARC
Editor in Chief

REFERENCE

1. Aerosol consensus statement. Consensus Conference on Aerosol Delivery. Chest 1991;100(4):1106–1109.

Consensus Statement: Aerosols and Delivery Devices

1. Delivery (Total and Regional) of Therapeutic Aerosols into the Lungs

An aerosolized medication is designed to be delivered through the airways within ventilated gas and then be deposited at sites in the lung through inertial impaction, gravitational sedimentation, and diffusion onto lung surfaces. The amount of aerosolized medication that deposits through these mechanisms in a given region in the lung depends on physical properties of the aerosol particle, ventilation factors, and regional airway anatomy/lung mechanics. Under ideal circumstances, lung deposition exceeding 50% of the aerosolized amount delivered to the patient can be achieved. In contrast, poor system designs and/or improper device usage can result in virtually no aerosol reaching desired sites in the lungs.

Physical properties of the aerosol affecting deposition include particle size, shape, and density. These are determined by the aerosol generator's performance characteristics (see below) and the aerosol formulation (ie, chemical and physical structure of drug, carrier [solvent], and/or propellant). Ambient humidity can be particularly important, as hygroscopic particles will increase in size as they flow through a moist airstream. Aerosol particles that can traverse the pharynx and upper airways are generally < 6 μm mass median aerodynamic diameter (MMAD). Aerosol particles that can traverse an artificial airway (eg, endotracheal tube) are generally < 2 μm MMAD. Once in the lungs, the smaller and less dense the particle, the more likely it is to penetrate into distal lung regions. Particles $<$ 0.6–0.3 μm MMAD often are exhaled, although "extra-fine" particles (< 0.1 μm MMAD) can diffuse out of the ventilatory air stream and ultimately settle on airway surfaces. Particle shape can also be important. Although current nebulizer technology involves primarily spherical droplets (solution aerosols), more aerodynamically designed particle shapes (eg, needle-shaped solid particles) conceptually could penetrate into very distal lung regions.

Ventilation factors affecting aerosol deposition include particle velocity, inspired volume, inspiratory time, breath-hold duration, and timing of aerosol delivery during inspiration. Particle velocity is determined by the aerosol generator (eg, pressurized metered-dose inhaler particle velocities range from 10–100 m/s, whereas current dry powder and jet/ultrasonic nebulizers produce aerosols with relatively low velocities) and is influenced by the patient/subject's inspiratory flow of aerosol-laden air. Typical adult inspiratory flows during quiet tidal breathing are approximately 0.25–0.5 L/s. Faster inspiratory flows increase oropharyngeal and upper airway deposition by inertial impaction; slower inspiratory flows minimize oropharyngeal and upper airway deposition and enhance more distal delivery and deposition through sedimentation and diffusion. Faster inspiratory flows (eg, 0.5–2 L/s) may be necessary with some dry powder systems to deaggregate and disperse the dry powder.

The size of the inspired volume influences deposition by affecting both the amount of aerosol that enters the lung and the depth of penetration of the aerosol into the lung. Breath-holding enhances deposition by facilitating sedimentation and diffusion. Breath-holding for at least 4 seconds appears important, although longer (eg, up to 10 seconds) may provide further benefit. Timing of aerosol administration during inspiratory flow will affect deposition. For example, delivery of the aerosol early in inspiration puts the aerosol at the "front end" of the breath for deeper penetration (although regions with airway closure at the beginning of inspiration may not receive such a "front loaded" aerosol). In contrast, delivery of the aerosol later in inspiration puts the aerosol at the "back end" of the breath-enhancing delivery to later-filling lung units.

Regional *airway anatomy/lung mechanics*, while not necessarily affecting total lung delivery, will affect regional deposition. In general, lung regions with poor ventilation due to air flow obstruction or low compliance will receive a lower volume of a delivered aerosol. Moreover, sharp airway branching angles, or impediments to air flow such as mucus accumulation or airway narrowing will enhance proximal airway aerosol deposition through inertial impaction and reduce more distal aerosol delivery in that region. In contrast, high-compliance units without reduced airway diameter will receive a higher volume of a delivered aerosol. It is important to remember that delivery and deposition, while related, are not necessarily linked. For instance, slower regional flows may reduce delivery but actually enhance deposition through sedimentation and diffusion. Complex computer models are needed to account for these multiple (often counteracting) effects in predicting regional aerosol deposition.

Aerosol drug targeting strategies attempt to utilize these deposition determinants along with a knowledge of receptor locations for specific drugs to place higher amounts of aerosol within desired regions. For example, drugs with site-specific actions on mucous glands and smooth muscle should be deposited in proximal airways (ie, the first 6 generations of the tracheobronchial tree), drugs affecting

inflammation in the airway epithelium should be deposited throughout the tracheobronchial tree, and drugs affecting alveolar function (both therapeutically as well as for maximizing systemic absorption) should be deposited distal in the alveolated regions. In addition, the use of monodisperse aerosols may allow a reduced dose of drug to be used.

The smaller size (number of airway generations, airway morphometry, gas volume, and surface area), rapid shallow breathing pattern (often with nasal breathing), and frequent cooperation difficulties in pediatric patients pose special problems for aerosol delivery. Specific requirements to improve pediatric delivery and deposition include production of smaller-particle aerosols, slower-velocity particles, and comfortable device interfaces with low dead space. Because so few aerosol dosing studies have been done in pediatric patients, adult doses are usually prescribed with the assumption that the expected reduction in delivery will result in appropriate dosing to the lung; however, the scientific basis for doing this is poor. Indeed, computer modeling has suggested that actual pediatric lung delivery can be quite variable and may be several-fold higher than in adults when drug deposition is referenced to lung surface area.

Because factors affecting deposition are so complex and difficult to predict, clinical studies with a new drug in the patients of interest should be required to determine safety/efficacy of a device and dosing strategy. Validated mathematical dosimetry models can aid in designing drug delivery protocols.

2. Aerosol Generators

There are 4 techniques to generate therapeutic aerosols: jet nebulizers, ultrasonic nebulizers, pressurized metered dose inhalers (pMDIs), and dry powder inhalers (DPIs). The pMDI can be used with or without a spacer/holding chamber. Jet and ultrasonic nebulizers can be used to create aerosols of many liquids, whereas the pMDI and DPI are always packaged with a specific medication. Table 1 lists advantages and disadvantages of aerosol-generating devices.

An important pMDI adjunct is the valved holding chamber, which allows improved coordination with patient inspiratory flow, reduces the overall particle size of the aerosol by causing larger particles to impact on chamber walls/valves, and reduces the "cold FREON" stimulus to premature inhalation termination. The particle velocity is also decreased and thus upper airway deposition is less. All of these effects can improve lung deposition from a pMDI.

Electrostatic charge in a plastic holding chamber can affect drug delivery by reducing output of larger particles. Electrostatic charge can be reduced by priming the chamber with the desired aerosol or by washing with ionic detergent and air drying. Although chamber design allows some delay, the aerosol should be inhaled immediately after the pMDI is discharged into the chamber and only a single actuation should be discharged into the chamber for each inhalation. In general, at least 15 seconds should separate individual pMDI discharges.

Valved holding chamber design needs to be reevaluated with new hydrofluoroalkane-propelled pMDI delivery systems, as particle behavior may be different. For example, it appears that some hydrofluoroalkane formulations produce a slower particle velocity with a higher aerosol temperature. Both of these are changes that will affect the quality of the aerosol spray.

The available evidence supports the safety and efficacy of nebulizers, pMDIs, and DPIs at the recommended drug doses. Because the pMDI and DPI delivery systems are the most convenient and provide the lowest cost/dose, they should be the first choice of clinicians. A valved holding chamber should be used with the pMDI whenever the patient cannot demonstrate acceptable hand-breath coordination and whenever pharyngeal deposition is of clinical concern (eg, inhaled steroids). In general, the valved holding chamber (often with mask) is almost always required in pediatric and geriatric populations. The nebulizer may be used if the drug is only available as a solution or if the pMDI/DPI cannot be used effectively. The nebulizer might also be used if a high drug dose is required (eg, continuous nebulization). Patient preference should also be considered when selecting an aerosol delivery device. It should be recognized, however, that patient preference for a nebulizer is often a consequence of higher (and often more appropriate) drug doses being used. Indeed, monitoring of patient response during dosing should be routine practice.

pMDI and DPI systems are underutilized in the United States in the acute care setting. Barriers to increased use of these devices should be identified and strategies developed to address these issues. One important barrier is the misconception of clinicians related to pMDI and DPI efficacy in this setting. Another important barrier in the United States is reimbursement, since many third-party payers reimburse for the nebulizer/drug package but not for the pMDI/DPI. Further, some risk-sharing capitative arrangements between providers and HMOs may likewise favor nebulizer use over pMDI/DPI systems. Educational efforts targeting clinicians (physicians, respiratory therapists, pharmacists, and nurses), patients, reimbursement agencies, and regulators are needed to address these issues.

Patient and health care worker education on proper use of delivery systems is important. Aerosol therapy should not be initiated without instructing the patient in the proper use of the device, proper handling, cleaning/disinfection, the expected effects and potential adverse effects of the drug, and the importance of patient adherence to a therapeutic regimen. pMDI efficacy is particularly user depen-

Table 1. Advantages and Disadvantages of Aerosol Generators and Delivery Systems

Type	Advantages	Disadvantages
Jet nebulizer	Patient coordination not required High doses possible No CFC release	Expensive Not portable—pressurized gas source required More time required Contamination possible Device preparation required before treatment Not all medications available Less efficient than other devices (waste)
Ultrasonic nebulizer	Patient coordination not required High doses possible No CFC release Small dead volume Quiet Faster delivery than jet nebulizer No drug loss during exhalation	Expensive Contamination possible Prone to malfunction Not all medication available Device preparation required before treatment
Metered-dose inhaler	Convenient Less expensive than nebulizer Portable More efficient than nebulizer No drug preparation required Difficult to contaminate	Patient coordination essential Patient actuation required Large pharyngeal deposition Difficult to deliver high doses Potential for abuse Not all medications available Many use CFC propellants
Metered-dose inhaler with holding chamber	Less patient coordination required Less pharyngeal deposition	More complex for some patients More expensive than MDI alone Less portable than MDI alone
Dry powder inhaler	Less patient coordination required Breath-hold not required Propellant not required Breath-activated	Requires moderate to high inspiratory flow Some units are single dose Can result in high pharyngeal deposition Not all medications available Difficult to deliver high doses

CFC = chlorofluorocarbon. MDI = metered-dose inhaler

dent and thus these educational issues are particularly important with these devices (Table 2). Because patient education is so critical to achieving the goals of aerosol therapy, it should be properly reimbursed.

The available evidence suggests that respiratory therapists can provide value in this area. Respiratory therapists can also implement protocols to increase the conversion of nebulizers to pMDI and DPI delivery systems and to reduce the misallocation of aerosol therapy.

The interface between the patient and the aerosol generator is also important in aerosol delivery. Patients should be instructed to inhale the aerosol through the mouth (rather than through the nose), although a physiologic response may occur with nasal inhalation of bronchodilators and steroids. An endotracheal tube or tracheostomy tube can significantly reduce lung delivery because of deposition in the tube, particularly with smaller-lumen neonatal or pediatric endotracheal tubes. Electrostatic charge and humidity can further decrease aerosol delivery through artificial airways.

A slow inspiratory flow and smaller aerosol particles improve aerosol delivery through the artificial airway. With the nebulizer, aerosol delivery is improved by moving the nebulizer to a point in the circuit closer to the ventilator. With the pMDI, aerosol delivery is improved by use of an in-line spacer/chamber device.

Aerosol system design can have significant impact on the amount and characteristics of the aerosol generated. Indeed, even among similar classes of device (eg, jet nebulizers, ultrasonic nebulizers, holding chambers), considerable variability can be demonstrated. Because of this, it is not appropriate to substitute one device for another without proper assessments (see below). For practicality and cost issues, it is often desirable to use a single system (eg, nebulizer or chamber) for multiple medications rather than multiple individual systems for

Table 2. Factors Important in Patient Instruction in the Use of pMDIs

pMDI issues	Shaking canister
	Priming new or infrequently used inhaler
	Removal of cap before treatment
	Holding canister upright
	Assessing when inhaler is empty
Holding chamber issues	Preparation of device (remove cap, attach inhaler)
	Single actuation into chamber
	Priming/cleaning issues
	Immediate inhalation after loading device
Patient issues	Breathing pattern (inspiratory flow, breath-hold)
	Time between each actuation
	Use only as prescribed

pMDI = pressurized metered-dose inhaler

each medication. Under these circumstances, however, it is incumbent upon the clinician to understand how each of the medications perform within that system, so as to assure proper dosing.

3. Pharmacology of Drugs Deposited in the Airways

Inhaled drugs offer advantages in the management of respiratory disorders because they are delivered directly to the intended site of action. As a consequence, lower doses (than for oral administration) are required for therapeutic effects, and systemic adverse effects are less than with systemic (eg, oral or intravenous) routes of administration. It is clearly desirable to have inhaled drug deposition in close proximity to the appropriate receptors. For example, bronchodilator medications need to be deposited close to their respective receptors in the airway, whereas antibiotics should be delivered to achieve high drug concentrations at the site of infection. Mathematical dosimetry, by knowing the amount of drug per unit inhaled volume and its particle characteristics, can assist in predicting the distribution pattern of an inhaled aerosol.

As noted above, a number of factors are involved in determining aerosol delivery and deposition in the lung. Once the drug deposits within the lung, its clearance is through one of 4 mechanisms.

(1) *Absorption into the blood stream.* This is a rapid process determined primarily by drug solubility, alveolar-capillary permeability, and regional blood flow. Aerosolized drugs designed to be delivered systemically (eg, insulin) should thus be targeted for distal alveolar regions where blood flow and surface area are high.

(2) *Local inactivation.* This is a slower clearance mechanism than absorption into the blood stream, and is accomplished through macrophage ingestion and local metabolic pathways.

(3) *Lymphatic clearance.* Drug absorbed into lung tissue but not cleared by regional blood flow will be more slowly cleared through lymphatic drainage.

(4) *Mucociliary transport.* Continuous transport of the aerosol drug up the mucociliary escalator into the posterior pharynx, where it is swallowed, occurs once the drug is deposited on the airway surface.

A broad range of β-adrenergic and anticholinergic bronchodilators, corticosteroids, and nonsteroidal anti-inflammatory agents are available as aerosols for treatment of asthma and chronic obstructive pulmonary disease (Table 3). Drugs administered as aerosols for treatment of pulmonary conditions other than asthma or chronic obstructive pulmonary disease include antibiotics and mucus active agents. Antibiotics with demonstrated efficacy when given by the aerosol route include pentamidine for *Pneumocystis carinii* infection prophylaxis and ribavirin for respiratory syncytial virus infection. Inhaled tobramycin aerosols are also of demonstrated efficacy in cystic fibrosis. Promising animal data and limited human data support the use of other antibiotics (ie, other aminoglycosides, colistin, polymixin, and amphotericin) in specific clinical settings. However, much larger human trials with appropriate clinical outcome measurements (see below) are required before broad clinical application can be recommended. Mucus active drugs administered as aerosols include dornase and *n*-acetyl cysteine. Dornase has been shown to be effective in improving sputum characteristics in cystic fibrosis. Data are limited for dornase in other hyper-mucus conditions (eg, bronchiectasis). Although effective in breaking up mucus when delivered as a bolus, *n*-acetyl cysteine has not been shown to be effective as an aerosol.

One use of aerosols is delivering pulmonary therapies with drugs that affect surface active function in lung parenchyma (ie, surfactant deficiency syndromes such as infant respiratory distress syndrome and surfactant dysfunction syndromes such as acute respiratory distress syndrome). A number of animal studies and small clinical studies using aerosolized surfactant show advantages over the instilled route (less fluid bolus effect, lower dosing), but broad clinical application awaits large randomized trials with appropriate clinical end points. Aerosolized surfactant may also improve airway function in chronic bronchitis and cystic fibrosis. Perflubron is another drug affecting lung surface active function, but it has not been studied as an aerosol.

There is growing interest in application of new and as yet experimental aerosolized therapies that have the potential to change the metabolic, oxidative, and genetic mi-

Table 3. Commonly Used Inhaled Drugs in the United States

Drug	Formulation	Dose	Number of Doses	Recommended Dosage
Bronchodilators				
Beta-adrenergic				
Albuterol	pMDI	90 mcg	200	2 doses 4–6 times/day
Albuterol SO_4	pMDI (HFA)	90 mcg	200	2 doses 4–6 times/day
Albuterol SO_4	DPI	200 mcg	1	1–2 capsules qid
Albuterol SO_4	solution	0.5%	unit	2.5–5 mg
Levalbuterol	solution	0.02/0.04%	1	0.63–1.25 mg
Metaproterenol SO_4	pMDI	650 mcg	200	2 doses 4–6 times/day
Metaproterenol SO_4	solution	5%	1	10 to 15 mg
Salmeterol xinafoate	pMDI	21 mcg	120	2 doses bid
Salmeterol xinafoate	DPI	50 mcg	60	2 doses bid
Pirbuterol acetate	pMDI/Autohaler	200 mcg	300/400	2 doses 4–6 times/day
Bitolterol mesylate	pMDI	370 mcg	300	2 doses tid
Bitolterol mesylate	solution	0.2%	1	0.5–3.5 mg
Anticholinergic				
Ipratropium bromide	pMDI	18 mcg	200	2 doses qid
Ipratropium bromide	solution	0.02%	1	0.5 mg
Combination				
Albuterol sulfate + ipratropium bromide	pMDI	100/18 mcg	200	2 doses qid
Anti-inflammatory				
Non-steroidal				
Cromolyn sodium	pMDI	0.8 mg	102/200	2 doses qid
Cromolyn sodium	solution	1%	1	20 mg qid
Nedocromil sodium	pMDI	1.75 mg	104	2 doses qid
Corticosteroids				
Beclomethasone dipropionate	pMDI	42, 84 mcg	80/200	2 doses qid/4 doses bid
Budesonide	DPI	200 mcg	200	1–2 doses bid
Flunisolide	pMDI	250 mcg	100	2 doses bid
Fluticasone propionate	pMDI	44, 100, 220 mcg	120	2 doses bid
Fluticasone propionate	DPI	50, 100, 250 mcg	4	2 doses bid
Triamcinolone	pMDI	100 mcg	240	2 doses tid or qid or 4 doses bid

pMDI = pressurized metered-dose inhaler. HFA = hydrofluoroalkane.

lieu of the lung. These therapies include anti-inflammatory agents, antiproteases, oxidative peptides, and other chemicals, as well as gene therapy for airway disorders, primarily cystic fibrosis. Other inhaled therapies that are still in the development phase include a variety of immunomodulatory drugs for the treatment of airway inflammatory and infectious disorders, and prostaglandins for treating pulmonary hypertension.

Finally, as noted above, the large blood supply of the lung (ie, virtually the entire cardiac output traverses the alveolar capillaries) makes aerosol delivery to the alveoli an attractive option for the systemic delivery of drugs. Drugs delivered in this fashion enter the arterial circuit directly and do not first pass through the hepatic beds, as orally administered drugs do. The most active clinical investigations involving this approach to systemic drug delivery involve insulin, but a number of other drugs (eg, analgesics) are also undergoing preclinical testing.

4. Assessing New Aerosol Systems—Scientific Issues

There are a number of steps to be taken in assessing the performance of aerosol delivery systems. In general, these involve using one of 3 end points:

A. Device delivery/deposition characteristics
B. Patient/subject physiologic response
C. Clinical outcomes

Assessing Device Delivery/Deposition Characteristics

A number of techniques are used to describe and quantify total/regional aerosol delivery and deposition. Termi-

Table 4. Definitions for Use in Aerosol Deposition Studies

Amount in nebulizer* = amount nebulized (emitted dose) + amount remaining in system
Amount nebulized* (emitted dose) = amount delivered to patient + amount deposited in tubing/device + amount released into atmosphere
Amount delivered to patient* = amount deposited in lung + amount deposited outside lung (eg oropharynx, gut) + amount exhaled

*Denominators used in "percent deposition"

nology used to describe doses measured must be universal and specifically defined in order to compare results between laboratories (Table 4).

In vitro measurements of emitted dose and particle size guide the user as to the likelihood of successful delivery of the inhaled medication to the lower respiratory tract. These measurements may also be used to assess equivalency of formulations and consistency of drug delivery. Standard methods for emitted dose and sizing measurements are described in the United States Pharmacopeia and published in Pharm Forum (Physical tests and determinations: <601> Aerosols, metered-dose inhalers and dry powder inhalers. United States Pharmacopeia 2000;25[Suppl 1]:2674–2688.) Using simulated breathing patterns and/or actual patient breathing patterns increases the reliability of the information obtained and the specificity to different clinical scenarios.

Inhaled dose and distribution of the inhaled dose can also be described with mathematical models. In the mathematical models, the choice of a geometric model to describe airway dimensions, along with the use of realistic air flow patterns and the incorporation of factors such as age and gender, should give results that more closely mimic experimental measurements. Correlations with in vivo data obtained under controlled breathing conditions and with stable aerosols indicate that the mathematical models can overestimate or underestimate regional deposition patterns, depending on the specific conditions being simulated. This is probably because of prescribed conditions such as the use of fixed breathing patterns, the use of stable, monodisperse aerosols, and the difficulty in properly modeling the airway geometry of disease states. Because of the complexity of the calculations, powerful workstations, sophisticated software, and experienced computer personnel are required, limiting the ability to model to certain institutions.

Physical models can also be used to assess aerosol delivery and deposition. These models can provide useful information, but, as with measurements to characterize the aerosol, they should include realistic breathing patterns and, where possible, incorporate changes in ambient conditions to simulate high humidity and high temperature environments.

In vivo measurements of dose delivered to animal and human lungs and distribution of the dose are also made using scintigraphic techniques that include rectilinear scanners, planar (two-dimensional) gamma scintigraphy, and the three-dimensional imaging methods, single photon emission computed tomography and positron emission tomography. Both planar and single photon emission computed tomography utilize low-energy gamma emitters, mainly ^{99m}technetium. Positron emission tomography tracers are isotopes of the basic biologic molecules—carbon, oxygen, fluorine, nitrogen, and neon—allowing functional imaging as well as deposition measurements. Table 5 lists the advantages and disadvantages of these techniques. With all these methods, the quality of the labeling procedure must be confirmed prior to use, including consistency in the dose of radioactivity inhaled. This requires measurements of emitted dose and the aerosol size distribution, in terms of both radioactivity and drug, to ensure that the radiolabel follows the drug in the radiolabeled product and that the drug is not altered by the labeling procedure. The latter requires in vitro comparison of the unlabeled product and the labeled drug product, and would allow clinical response measurements obtained post inhalation to be correlated with deposition.

Pharmacokinetic methods can also be used to measure the pulmonary deposition of aerosolized drugs that are not metabolized in the lung and are not absorbed via the gastrointestinal tract. Assuming complete drug absorption across the alveolar capillary interface, systemic bioavailability of the drug equals pulmonary bioavailability. Intravenous administration of a known amount of drug labeled with an isotope as an internal standard allows an absolute estimation of the pulmonary deposition of the drug from the appearance of the labeled and unlabeled compound in plasma/serum and urine. For drugs that are absorbed in the gastrointestinal tract, this method can also be used, provided a slurry of charcoal is pre-administered to the subject to block gastrointestinal absorption.

Intermediate Physiologic and Clinical Responses of Animals and Human Subjects

Intermediate physiologic and clinical responses of animals and human subjects are end points that are based on measurements readily obtained in the experimental or clinical setting (Table 6). They are often considered "surrogate" measurements for the ultimately desired clinical outcome. Commonly used measurements when assessing airway active drugs include a variety of pulmonary function tests that are usually reflective of the drug's mechanism of action (eg, change in forced expiratory volume in the first second as a reflection of bronchodilation). Other

Table 5. Advantages and Disadvantages of Positron Emission Tomography Versus Other Techniques

Advantages	Disadvantages
Three-dimensional information	Requires proximity to a cyclotron for manufacturing positron emission tomography emitters
Resolution 4–5 mm; can divide the lung into 120 slices	Specialized radiochemistry
Measures biologic activity and drug distribution	Initial equipment costs high
Tissue attenuation coefficients for radioactivity measured directly	Substantial operating costs
Greater sensitivity and accuracy than two-dimensional or single photon emission computed tomography	Greater radiation dose and exposure than two-dimensional planar imaging
Serial measurements within the same day are possible	
Sites of lung uptake of (radiolabeled) drug can be visualized	

measurements, depending on the drug's desired effect, could include protection against bronchoconstrictive stimuli, gas exchange, cardiac function, blood/tissue sampling, and other assessments of metabolism and physiology.

Clinical Outcomes Assessment

Clinical outcomes assessment uses end points that are direct evaluations of a desired clinical benefit. Examples are listed and commented on in Table 7. Studies using these types of end points are generally more complex and expensive to perform. Nevertheless, it is only with these types of end points in randomized clinical trials that the clinically important benefit of an aerosolized drug system can be properly assessed. As newer drug products/aerosol systems become more expensive, third-party payers are likely to demand improvements in clinically relevant outcome end points, even if regulatory approval has been obtained using intermediate end points.

5. Assessing New Aerosol Systems—Regulatory Issues

The regulatory process is concerned with establishing safety and efficacy of drugs and devices. Initial assessments of safety and efficacy are usually done with in vitro and animal studies using the end points described above. These studies are then followed by clinical trials, again using any or all of the end points noted above. Clinical trials generally are conducted in 3 phases: Phase I assesses safety and dosing regimens in small populations; Phase II assesses safety and efficacy in potential patient populations; Phase III is the definitive controlled trial using the optimal dose/device in the target population.

From a regulatory perspective, safety is assessed by considering adverse events during any phase of the evaluation process. Of particular concern are "serious adverse events" (ie, the patient outcome is death, is life-threatening, requires or prolongs hospitalization, produces persistent or permanent disability, produces a congenital abnormality, or there is a requirement for medical intervention to prevent these occurrences). Safety assessments for both drugs and devices continue beyond the clinical trials process, and usually include 12–18 months of post-marketing approval surveillance (Phase IV evaluations). Because a newly marketed drug or device is always introduced to a larger and more heterogeneous population than that treated during the clinical trial(s), new safety issues may appear during the first few years that a product is on the market.

Efficacy can be established using any of the end points described above. However, from a regulatory perspective, end points with clinical relevance derived from controlled human studies are required for any new aerosol drug system. In these studies, the new aerosol drug system can be compared either to placebo (usually the case with a new product) or to an existing product intended for similar use. Unfortunately, demonstrating a clear, statistically significant clinical benefit is not always easily accomplished in a patient population with variable disease manifestations. It is thus critically important to assure that the evaluation is properly powered statistically.

In September 1994, the United States Food and Drug Administration informally issued guidelines for "clinical development of new inhalation drug products and changes

Table 6. Potential Intermediate (Physiological) End Points

Pulmonary function (spirometry, lung volumes, diffusion)
Gas exchange
Exercise tolerance
Mucus/sputum characteristics/volume
Radiology
Tissue samples
Blood samples

Table 7. Potential Clinically Relevant Outcome End Points

Symptoms
Toxicity
Health care costs
Quality of life
Morbidity

Table 8. Cost-Benefit Elements Relevant to Aerosol Therapy

Costs	Research and development of drugs and devices
	Costs of marketing and supply
	Monetary cost to patient
	Drug
	Device
	Maintenance and repair
	Caregiver time for education and administration
Benefits	Physiologic benefit (eg, FEV_1)
	Symptomatic benefit (eg, dyspnea)
	Functional benefit (eg, activities of daily living, walk distance)
	Improved adherence to medications (eg, because of patient preference, ease of use)
	Quality of life
	Morbidity and resource use (eg, emergency department visits, hospitalization)
	Mortality

FEV_1 = forced expiratory volume in the first second

in formulation and/or device of existing approved inhalation drug products." In addition to appropriate in vitro and animal testing, this document recommended randomized controlled human clinical trials with appropriate end points not only to demonstrate safety and efficacy of new aerosol drug systems but also to demonstrate equivalency of new devices to old devices (when packaged with the drug as a single product), new propellants to old propellants, and pMDI to DPI. These guidelines are appropriate for new aerosol drug system development or when there is reason to believe that a change in drug formulation, integrated delivery device, or propellant could have significant impact on safety and efficacy. In contrast, auxiliary devices not integral to the drug package but designed to accept manufacturers' actuators are assessed through the Food and Drug Administration "510k" process, which requires only that new devices be shown to be "substantially equivalent" to existing devices using in vitro testing.

Two other recent regulatory developments in the United States deserve additional comment. First, in accordance with the Montreal Agreement to ban the use of ozone-depleting substances, the Food and Drug Administration has developed a reasonable plan to phase out ozone-depleting chlorofluorocarbons in pMDIs, as acceptable alternatives are developed. It is important that all patients are adequately served by these replacements before the original chlorofluorocarbon-powered pMDI is permanently banned.

Second, as noted above, pediatric aerosol dosing strategies are usually extrapolated from adult-derived safety and efficacy data. Recent federal mandates, as well as good clinical management, demand that specific pediatric data be generated to more properly define these strategies. It is inappropriate, however, to expect manufacturers to bear sole responsibility for funding and accepting liability for these studies. Instead, consortiums of manufacturers and third-party payers (including governmental agencies such as the National Institutes of Health, Food and Drug Administration, and Health Care Financing Administration) should be formed to undertake research in this area.

6. Cost Issues

Cost is a measure of resource consumption. In applying cost data to aerosol therapy, both direct and indirect costs should be considered, as should those elements of cost that are variable versus fixed. All relevant costs to the patient and to the health care system should be considered. Similarly, outcomes used in cost-benefit analyses should be relevant (Table 8). At present there is a serious lack of definitive data regarding cost-effectiveness and cost-benefit of aerosol therapies.

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Influence of Inspiratory Flow Rate, Particle Size, and Airway Caliber on Aerosolized Drug Delivery to the Lung

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Deposition Mechanisms: Inspiratory Flow Rate and Particle Size
Aerosol Delivery to the Lung
Sources for Obtaining Aerosol Deposition Information
Airway Caliber
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Aerosol Deposition and Response: Influence of Inspiratory Flow Rate and Particle Size
Nebulizers
Modelling In Vivo Delivery of Aerosol
Summary

[Respir Care 2000;45(6):597–608] *Key words: particle size, inspiratory flow rate, scintigraphy, metered-dose inhaler, lung deposition, emitted dose, fine particle dose, drug targeting.*

Introduction

The effect of various factors, such as aerosol size and density, inspiratory flow rate (IFR) and volume, and mean residence time in the lung, on the site of deposition in the lung have been studied extensively using both tracer and clinical aerosols.[1,2] These types of studies have provided a scientific basis for estimating drug delivery to the lung, site of action of drug within the lung, and drug dosage requirements. The advantage of quantitating deposition using imaging techniques following inhalation of a radiolabeled drug aerosol, performed in conjunction with pharmacodynamic and/or pharmacokinetic measurements in the same subject and carried out at the same time as the imaging studies, is obvious, and this would be the ideal approach in determining the response to a therapy inhaled from a pressurized metered dose inhaler (pMDI), a dry powder inhaler (DPI), or a nebulizer.

Delivering aerosols to the lung is a combination of drug formulation, delivery system properties, the patient's inhalation technique, and the geometry of the airways. Fine particle low-velocity aerosols carry drug more deeply into the lung; hence removal of the drug from the lung by mucociliary clearance may be slower[3] and the absorption of the drug from airway surfaces into the systemic circulation, partly a function of surface area, may be increased, compared to drug deposited more proximally.[4–6] These differences can ultimately lead to improved clinical responses to the aerosolized therapy, but can also give rise to increased adverse effects. Developing aerosol delivery systems incorporating the two key factors, along with ease of use, portability, and patient compliance aids such as dose counters and integrated electronic management systems to track treatments and treatment schedules, drive the innovations in inhaler design and potentially provide novel drug delivery systems.

Deposition Mechanisms: Inspiratory Flow Rate and Particle Size

Impaction, sedimentation, and diffusion are the main physical mechanisms governing deposition of inhaled drug

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Table 1. Deposition: Factors and Effects

Aerosol size, air flow rate, airway caliber
Drug dose inhaled (quantity, quality)
Site of deposition
Lung absorption
Clinical response

particles and droplets.[7] Though particle diameter is the primary factor determining the relative contribution of each process to the total amount deposited, the IFR also plays an important role in influencing deposition efficiency, regional distribution of the aerosol within the lung, and portioning of the inhaled dose between the upper and lower respiratory tract (Table 1). Particle velocity (the rate at which particles travel through the airways) varies with both the IFR and airway diameter:

$$v = IFR/A, cm/s$$

where A = airway cross-sectional area, in $cm^2 = d^2/4$ and d = airway diameter, in cm.

As IFR increases or airways narrow, air velocity and turbulence increase. This affects particle movement and increases deposition onto airway surfaces, particularly at airway bifurcations. Asymmetric velocity profiles have been observed on both inspiration and expiration, with secondary flows produced in subsequent airway generations.[8] These secondary, turbulent flows cause the maximum velocity of the incoming air to lie adjacent to the inner walls of the airway and close to the mucus layer, thus favouring deposition of particles along the airway wall. Deposition can occur during both inspiration and expiration, as demonstrated by Smaldone et al.[9]

Aerosol Delivery to the Lung

IFR can also influence the drug dose dispensed from an inhaler, the amount inhaled, the amount deposited in the oropharynx, the site of deposition in the lung, and, indirectly, the absorption of drug from the lung into the systemic circulation. A number of studies have shown that differences in the site of deposition of a drug can modulate the clinical response.[10–12] It is worth noting that the relative importance of the variables associated with the inhalation maneuver may differ for different drug delivery systems. For example, breath-actuated systems usually require higher IFRs than inhalation from a pMDI with spacer, so one should expect to see differences in bioavailability[13,14] related to the differences in dose inhaled and where the drug is deposited in the lung.[15]

Table 2. Scintigraphic Methods

Non-imaging
NaI crystal detector
Rectilinear scanner
Planar—2-dimensional
Anger camera
Rectilinear scanner
Tomography—3-dimensional
SPECT (single photon emission computed tomography)
PET (positron emission tomography)

Sources for Obtaining Aerosol Deposition Information

Information describing deposition in the lung can be obtained through computer modelling using theoretical calculations[16] or empirical models.[17,18] Experimental data are obtained using in vitro models, in vivo radioisotope studies, pharmacokinetic studies, and experiments measuring the recovery of inhaled boluses of tracer aerosols. Experimental studies have been performed in animal models and in humans, both normal healthy subjects and patients with varying severities of lung disease. Because of the inter-individual variability in lung geometry, patterns of breathing, and the different methods used to obtain deposition data, models for predicting dose inhaled and deposited are still not fully predictive.

Table 2 lists scintigraphic methods to detect the distribution of an inhaled radiolabeled aerosol. These include both nonimaging and imaging techniques, the latter being either two-dimensional (planar) or three-dimensional (single photon emission computed tomography [SPECT] or positron emission tomography [PET]).[19] Both planar and SPECT employ relatively low-energy gamma emitters (^{99m}technetium or ^{131}iodine), whereas PET uses high energy positron emitters and applies coincidence counting to detect two oppositely charged gamma rays of 511 kiloelectron volts.

The images obtained using two-dimensional or three-dimensional scintigraphic techniques provide a detailed visual picture of where drug deposits in the lung, and the calculation of inhaled dose using two-dimensional imaging is used in a number of laboratories. However, the lung is a three-dimensional structure, and with two-dimensional planar imaging the distribution of a radio-tracer can only be viewed in two dimensions. Indeed, the contribution from overlapping small airways in the hilar region can be considerable,[20] resulting in an overestimation of central airway deposition and, in some cases, also peripheral deposition. This source of error can be reduced by using three-dimensional techniques such as SPECT[21,22] and PET,[23] which allow a more accurate measurement of deposited dose within the lung. Other drawbacks in imaging a three-

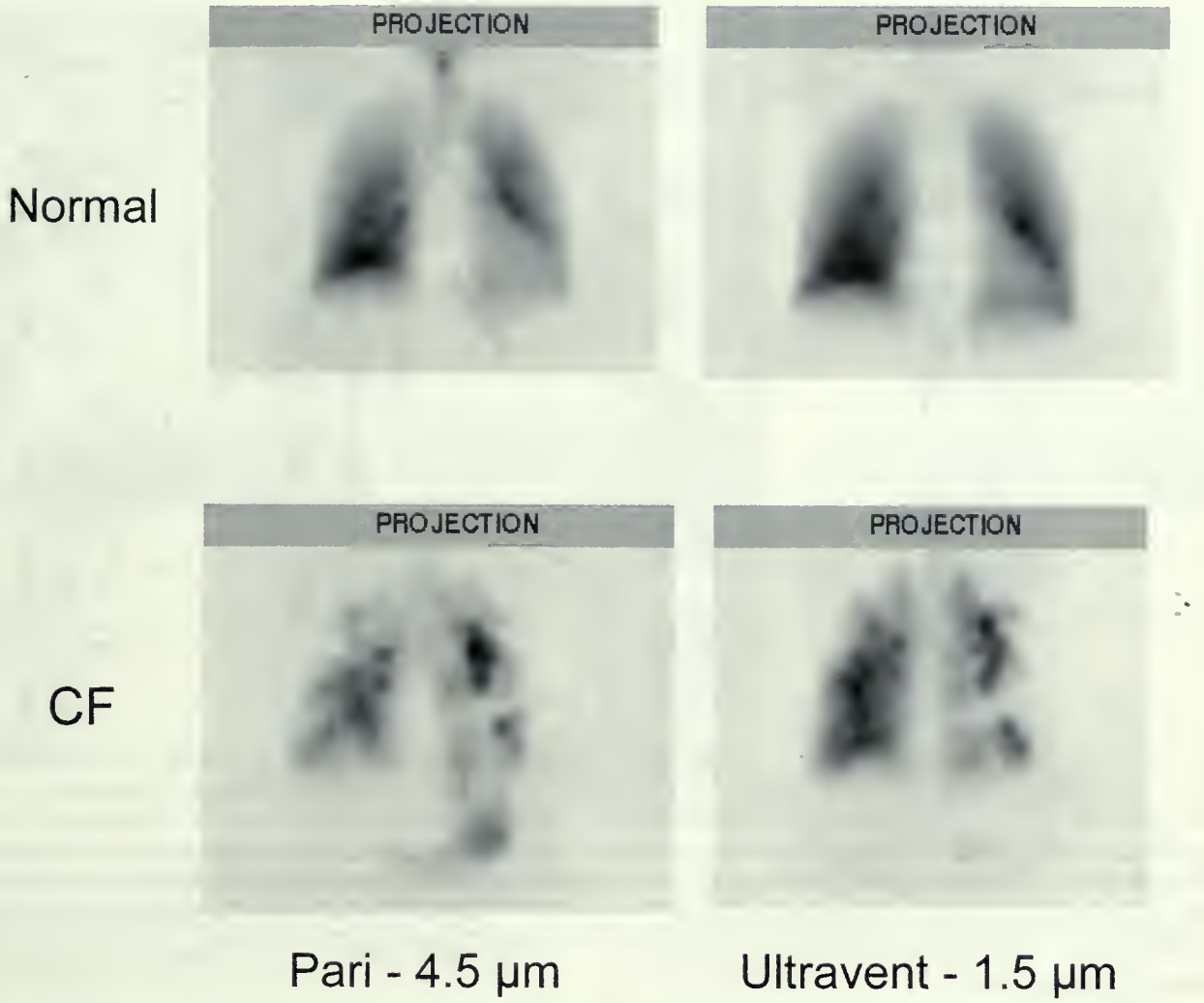

Fig. 1. Projection views from a normal subject and a subject with cystic fibrosis acquired after inhaling aerosols of 4.5 μm and 1.5 μm MMAD. These views represent the cumulation of data from 120 individual images from the coronal plane of the PET scan and are similar to what would be represented by the two-dimensional gamma camera.

dimensional object in two dimensions include the resolution and an accurate correction for attenuation of the radioactivity by the chest wall. SPECT and PET overcome these issues. With PET in particular, the acquisition of the transmission scan immediately after the PET investigation and with the patient in the same position under the scanner provides much greater accuracy for correction of the data for attenuation. In addition, for each slice in each of the 3 planes, the emission scan is paired with its own transmission scan, allowing the outline of that lung slice to be applied precisely to locate the regional emission data. This also allows the correction for tissue attenuation of radioactivity to be applied specifically to each emission slice. There are a limited number of studies with inhaled SPECT and PET tracers published in the literature, using both nebulizers and DPIs to administer the PET tracers.[24–28]

Figure 1 shows projection views and Figure 2 shows a series of images (slices) taken from a PET study estimating deposition of 1.5 μm and 4.5 μm aerosols in normal subjects and in patients with cystic fibrosis. The projections are the summation of all slices in the coronal plane and would be similar to what would be acquired with the two-dimensional gamma camera. It can be seen that the detail provided in the coronal slices is lost in the projection view. The calculation of deposited dose from the two-dimensional image is based solely on the information from the projection view, whereas with PET and SPECT there is the additional ability to calculate dose per slice. For example, in the CF subject, it can be seen in Figure 2B that though there is considerable impaction of the fine aerosol, the very anterior and posterior areas of the right lung are ventilated. Regional analysis of deposition, calculated for each slice and plotted versus distance through the lung, is based on data from each slice defined by the lung geom-

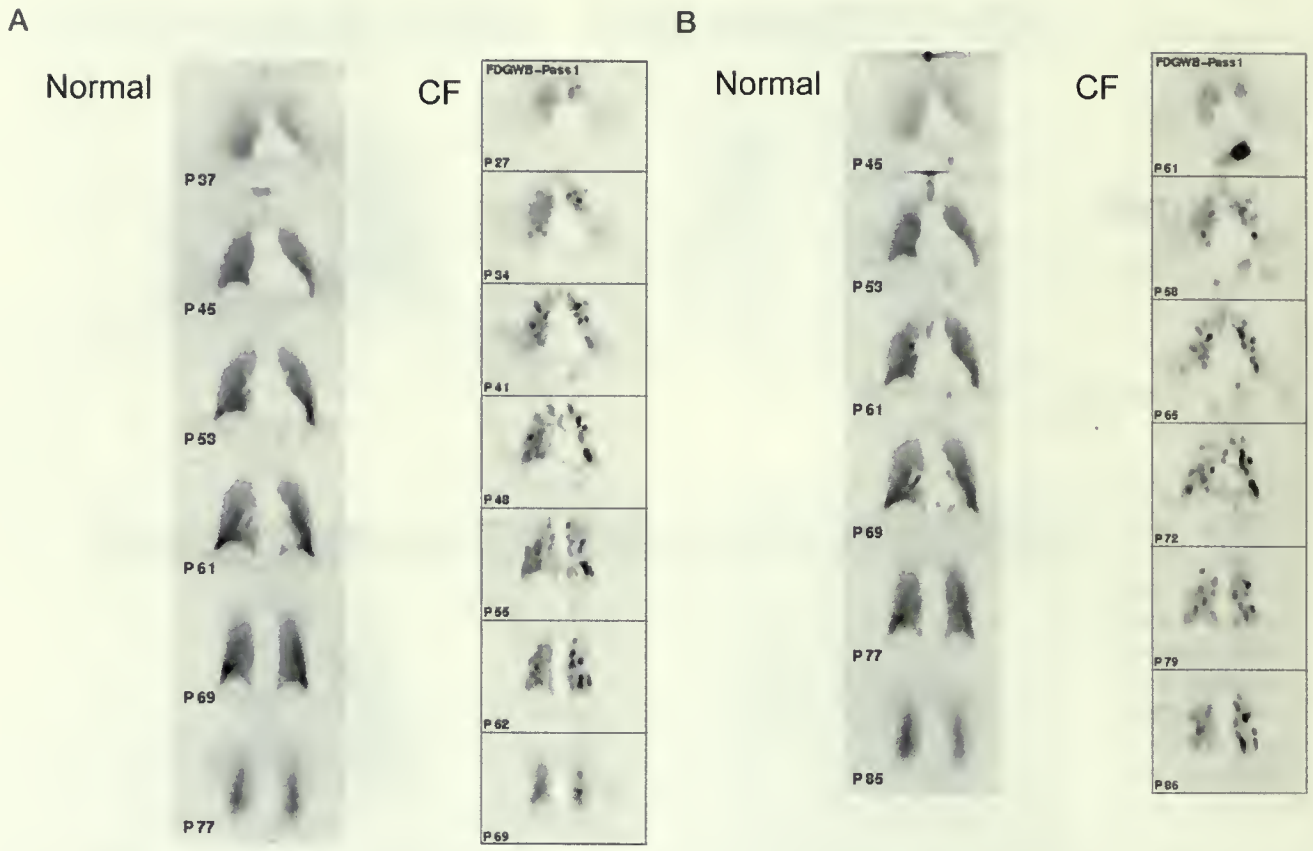

Fig. 2. A sample of coronal slices. A: Images from normal subject (left column) and cystic fibrosis subject (right column), showing the detail of the distribution of the aerosol inhaled ^{18}fluorodeoxyglucose generated by an Ultravent jet nebulizer (mass median aerodynamic diameter = 1.5 μm). B: Normal subject (left column) and cystic fibrosis subject (right column) showing the detail of the distribution of the aerosol inhaled ^{18}fluorodeoxyglucose generated by the Pari LC Star jet nebulizer (mass median aerodynamic diameter = 4.5 μm). With this imaging system, the detail is greater than that available from two-dimensional imaging, allowing greater accuracy in measuring dose and regional distribution of inhaled drug.

etry and regions of interest for that slice, and thus provides greater accuracy in the calculation of dose. The other two planes available with three-dimensional imaging, the transaxial (Fig. 3) and sagittal planes, similarly provide valuable information about dose deposited and site of deposition of aerosol.

Airway Caliber

Regional distribution of aerosol in the lung is also influenced by the caliber of the airways (Fig. 4).[7,29–32] The degree of airway narrowing, whether due to inflammation, bronchoconstriction, or the presence of increased secretions, can have a profound effect on where aerosol particles deposit. This can be seen in Figure 2B, where the images from the cystic fibrosis patient are patchy, containing many hot spots of radioactivity deposited at points of airway narrowing in the lung. This is despite the inhalation of a fine (< 2 μm) aerosol. Whether the improvement in distribution compared to the images obtained with a 4.5 μm aerosol would be sufficient to effect a more favorable clinical outcome is not yet known.

In contrast, as shown in Figure 5, changes in airway caliber effected with inhalation of a bronchodilator will alter the pattern of deposition, with the aerosol penetrating to lung distal to the site of obstruction.[33]

Particle Size Distribution

Methods for measuring the aerodynamic size distributions of aerosols used for inhaled therapy are well described in the literature and allow prediction of deposition efficiency and behaviour of the drug in the lung.[34,35] The estimation of deposition efficiency for these aerosols is usually based on the mass median aerodynamic diameter (MMAD), a statistical measure of the particle size distribution that characterizes the aerosol in terms of its mass (50% of the mass of the aerosol residing in particles less than the MMAD and 50% in particles greater than the MMAD) and the geometric standard deviation, although the latter is less

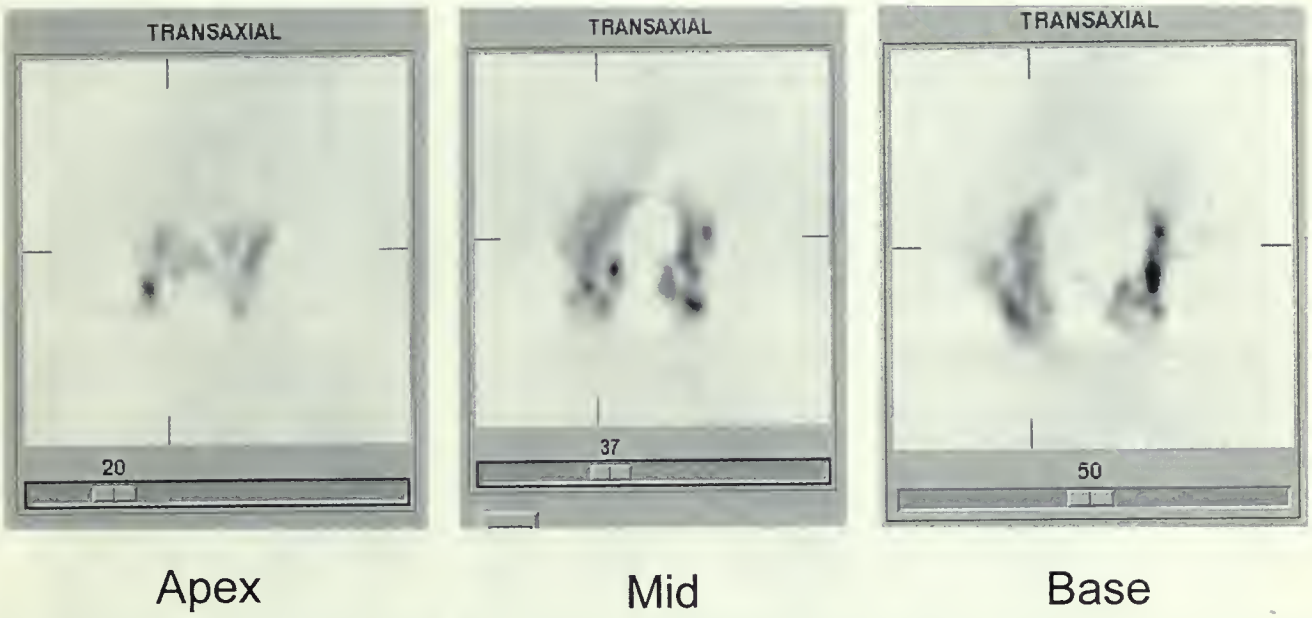

Fig. 3. Transaxial slices from the apex, middle, and base of lungs, showing the distribution of inhaled ^{18}fluorodeoxyglucose aerosol from a Pari LC Star jet nebulizer (mass median aerodynamic diameter = 4.5 μm) in a subject with cystic fibrosis.

predictive than the MMAD and other factors described below. In addition to obtaining these values from the mass-size distribution plot, the dose of drug available within defined size ranges can be determined from impactor/impinger sizing measurements, enabling a more precise prediction of drug delivery to various sites in the lung.

Both theoretical calculations and actual measurements have indicated that particles > 6 μm deposit in the oropharynx, particles between 2 μm and 6 μm deposit in the central airways, and particles < 2 μm deposit at more distal sites in the lung (the peripheral airways). If there is a percentage of particles within the aerosol that is finer than 1 μm, a portion will be exhaled or will be trapped in the residual air and eventually deposited on the respiratory bronchioles and perhaps on alveolar surfaces. The fraction of the aerosol containing particles < 5 μm (sometimes defined as < 6 μm) in diameter is termed the fine particle or respirable fraction (FPF), and has been used more widely recently to describe the quality of the aerosol and its potential for delivery to the lower respiratory tract.

The emitted dose (ED), the FPF, and fine particle dose (FPD = FPF $\times$ ED $\times$ 100%), the coarse particle fraction (CPF, percent of particles > 5 μm) and coarse particle dose (CPD = ED $\times$ CPF $\times$ 100%) of the dispensed aerosol are all affected by the flow of air drawn through the inhaler. An extra-fine particle fraction (EFPF) and extra-fine particle dose (EFPD) has been defined for those aerosols whose distributions contain a majority of particles $<$ 1 μm in diameter. All these fractions increase or decrease, depending on the in vitro test flow of the sizing system used to measure the quality of the aerosol or the in vivo IFR used during a patient inhalation maneuver.[36–38] For example, a critical step in dispensing a dose from a passive DPI (ie, DPIs that require inspiratory effort from the patient to dispense the powder from the device) is the process of deaggregating the powder clump. This is a function of the energy applied to the powder (ie, the inspiratory effort exerted by the patient). Too weak an effort (low IFR) will not fully aerosolize the powder, resulting in a lower dispensed dose, less drug inhaled, and reduced response.[37,39] In addition, the powder cloud will behave as a large-particle aerosol, with a higher CPF (lower FPF).

Table 3 shows the difference in in vitro FPFs when sampled at high and low IFRs for several passive DPIs.[38] Data are also shown for the Ventolin pMDI used with the Volumatic spacer, to illustrate these changes for a pressurized aerosol in comparison to a powder. All the DPIs listed yield powder aerosols with increased FPFs and, hence, increased FPDs when inspiration is performed at the higher IFR. Deposition is maximal in the central airways because of the increased IFR. However, with the increased dose to the lung,[40] clinical efficacy is greater.[41] In contrast, the FPF for the finer pMDI aerosol dispensed from the spacer decreases, reflecting increased impaction of aerosol on the spacer valve and walls with the higher sampling flow. A number of studies, in both children and adults, have measured the effect of IFR on lung deposition and clinical response from pMDIs and DPIs; in general, results indicate flow-dependence in both deposition and response.[41,42]

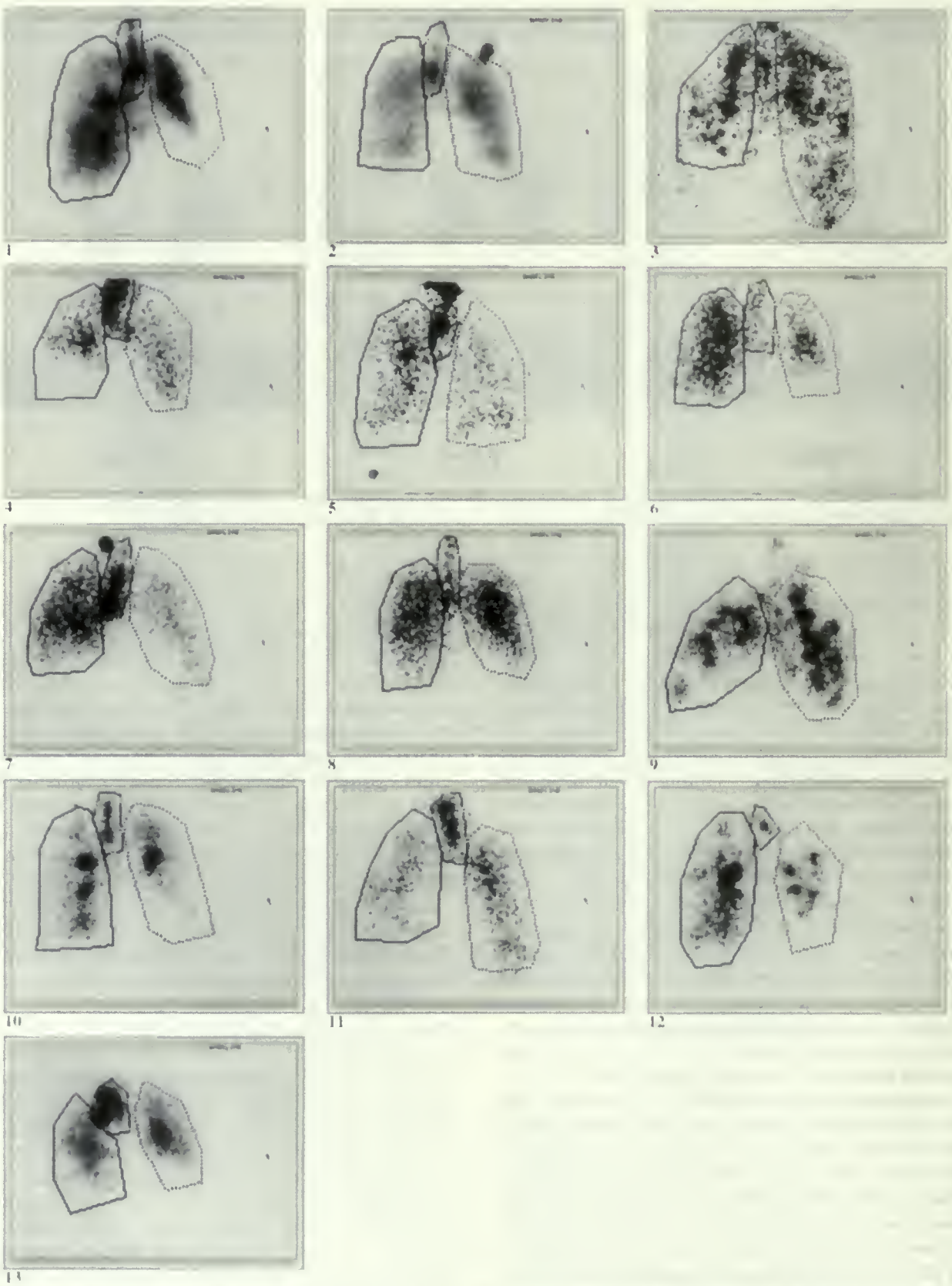

Fig. 4. Anterior scans for 13 critically ill but stable subjects receiving mechanical ventilation. Aerosol appears to be distributed more centrally in the subjects with chronic obstructive pulmonary disease. (#3, 9, 10, 12, 13) (From Reference 30, with permission.)

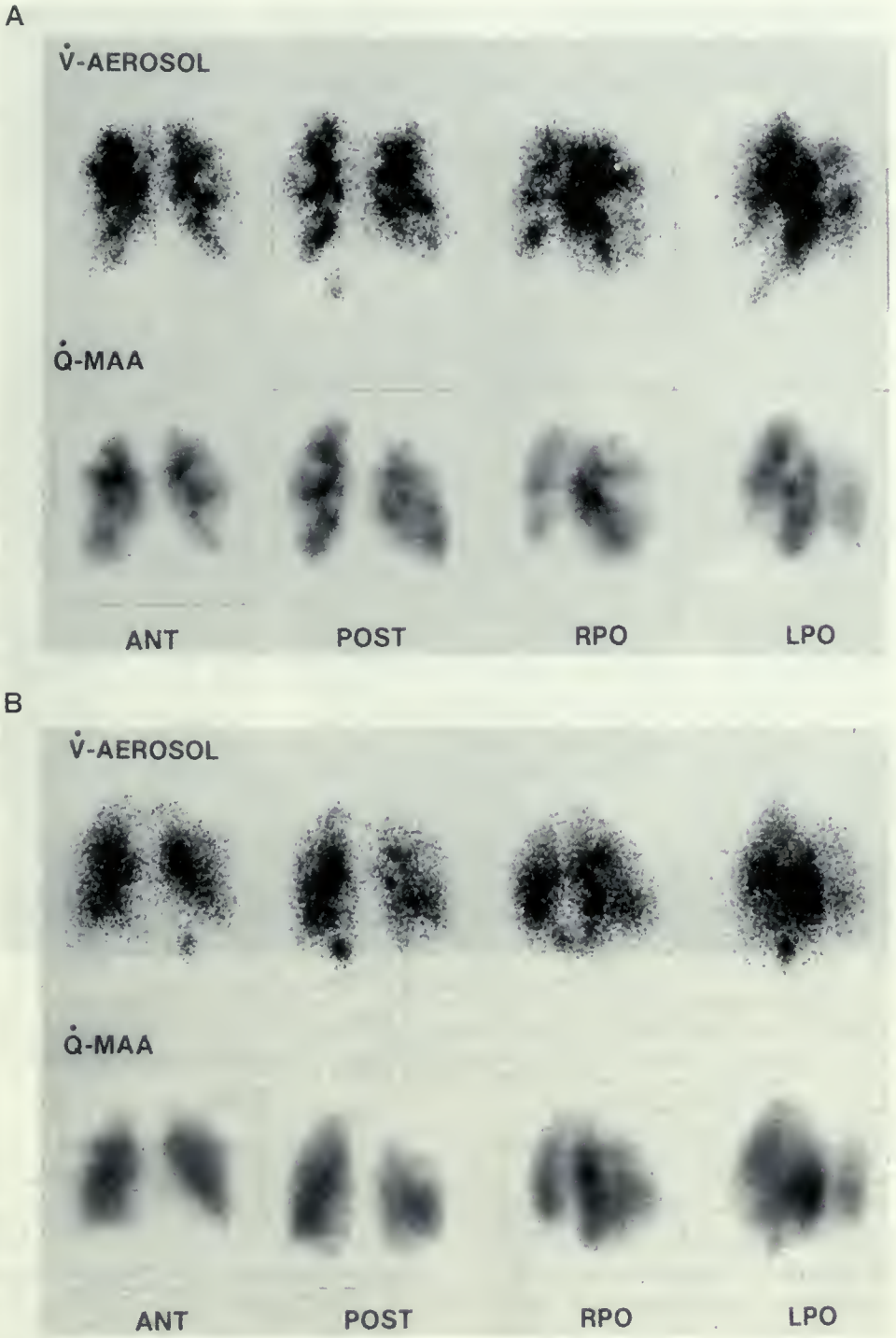

Fig. 5. Ventilation/perfusion ($\dot{V}/\dot{Q}$) scans from an asthmatic patient with acute shortness of breath, obtained (A) before bronchodilator therapy and (B) after bronchodilator therapy. The 4 views in the upper row of Figure 5A show that the deposition pattern is patchy because of airway narrowing and increased air flow turbulence. Matching decreases in perfusion can be seen in the views in the lower row of Figure 5A. In Figure 5B, ventilation and perfusion are more uniform following inhalation of bronchodilator.

Table 3. Comparison of Fine Particle Fractions of Salbutamol Delivered from Various Inhalers as a Percent of Label Claim

Inhaler	Nominal Dose	FPF (% LC) at 28.3 L/m	FPF (% LC) at 60 L/m
pMDI + Volumatic	100 μg/puff	68.9 ± 12.2	58.2 ± 6.6
Diskus	200 μg/blister	23.3 ± 0.9	31.6 ± 0.9
Diskhaler	200 μg/blister	20.4 ± 8.6	26.9 ± 5.7
Turbuhaler	100 μg/dose	13.3 ± 1.6	27.6 ± 8.0
Turbuhaler	50 μg/dose	9.7 ± 3.2	23.3 ± 3.0

FPF = fine particle fraction. LC = label claim. pMDI = pressurized metered-dose inhaler. All values are expressed as means ± standard deviation.

Table 5. Inspiratory Effort or Inspiratory Flow Rate and Inhaler Performance

Inspiratory Flow Rate Affects
Particle size distribution: fine particle fraction, coarse particle fraction
Dose dispensed
Loss of drug in inhaler
Fine particle dose, coarse particle dose
Dose inhaled
Oropharyngeal dose
Lung dose
Distribution of the inhaled dose in the lung
Central vs peripheral deposition
Clinical response

The ratios of FPDs to CPDs can also be used to compare aerosol formulations, as well as to assess the extent of changes to an aerosol by a delivery device (eg, pMDI with a spacer).[43–46] Table 4 shows the increase in FPD and decrease in CPD for hydrofluoroalkane (HFA)-134a-propelled beclomethasone dipropionate (QVAR), compared to the chlorofluorocarbon-propelled formulation of the same drug (Beclovent). The F_f/F_c ratio (a comparative index of overall effectiveness for the two aerosol formulations) indicates a two-fold overall change in the quality of the aerosol, effected by the changes in propellant and redesigned canister hardware to accommodate this new formulation. A number of in vivo deposition studies have shown 3–10-fold higher deposition with QVAR than with Beclovent,[47,48] with a 2.5:1 improvement in clinical outcomes for the same prescribed drug dose.[49]

Table 4. Comparison of Fine Particle Dose and Coarse Particle Dose Ratios for QVAR Hydrofluoroalkane-Propelled-Beclomethasone Dipropionate and Beclovent Chlorofluorocarbon-Propelled-Beclomethasone Dipropionate*

F Ratio	QVAR	BV	QVAR/BV
FPD Ratio (Ff)	17.62 μg	12.61 μg	1.40
CPD Ratio (Fc)	23.39 μg	33.91 μg	0.69
I (Ff/Fc)	1.40	0.69	2.03

F Ratio = the fraction of the fine or coarse dose emitted from QVAR, compared to BV.
QVAR = 134a-propelled beclomethasone dipropionate.
BV = Beclovent chlorofluorocarbon-propelled-beclomethasone dipropionate.
FPD Ratio = fine particle dose ratio (the mass of the emitted dose contained in particles < 4.7 μm aerodynamic diameter for QVAR divided by that for BV).
Ff = fine fraction = FPD of QVAR divided by FPD of BV.
CPD Ratio = coarse particle dose ratio (the mass of the emitted dose contained in particles > 4.7 μm aerodynamic diameter for QVAR divided by that for BV).
Fc = coarse fraction = CPD of QVAR divided by CPD of BV.
I = Ff/Fc = comparative index of overall effectiveness for the 2 aerosol formulations.
*Calculated from Anderson Cascade Impactor data collected at 28.3 L/m.

Aerosol Deposition and Response: Influence of Inspiratory Flow Rate and Particle Size

The dose of aerosol deposited in the lung is a fraction of what is inhaled, and that inhaled dose is, in turn, a fraction of the nominal or "label claim" dose specified by the pharmaceutical company on the package. Estimates of inhaled doses are based on the FPF (percent of particles < 4.7 μm or < 5.8 μm in diameter) of the aerosol and the emitted or inhaled dose of drug from the delivery system. Drug deposition in the lung is reduced because of drug deposition in the device and in the oropharynx, which varies depending

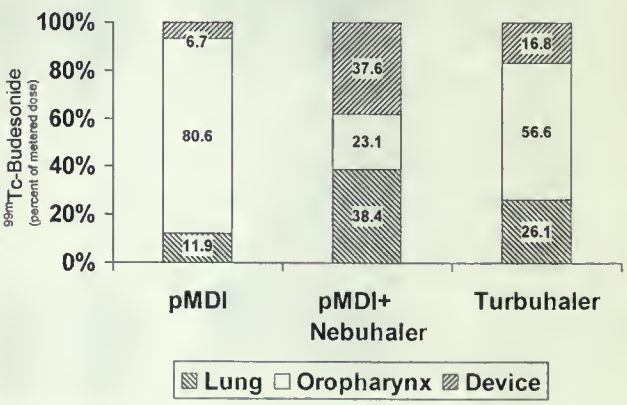

Fig. 6. Dose deposition of ^{99m}technetium (Tc)-budesonide in the lung, oropharynx, and device, in a study with 8 adult asthmatics, comparing pressurized metered-dose inhaler (pMDI) with pMDI-with-Nebuhaler valved holding chamber (VHC) and with Turbuhaler. Greater lung deposition was obtained with the pMDI-with-Nebuhaler than with either the pMDI alone or the Turbuhaler, most likely because of the combination of the lower IFR used to inhale the aerosol (16 L/m with the pMDI-with-Nebuhaler, 28 L/m with the pMDI alone, 67 L/m with the Turbuhaler) and the finer aerosol particles available from the VHC. The coefficient of variation for the lung deposition measurement is also less with the pMDI-with-Nebuhaler (27%) than with the pMDI alone (42%) or with the Turbuhaler (40%), suggesting a more reproducible execution of the inhalation technique. (Adapted from data in Reference 51).

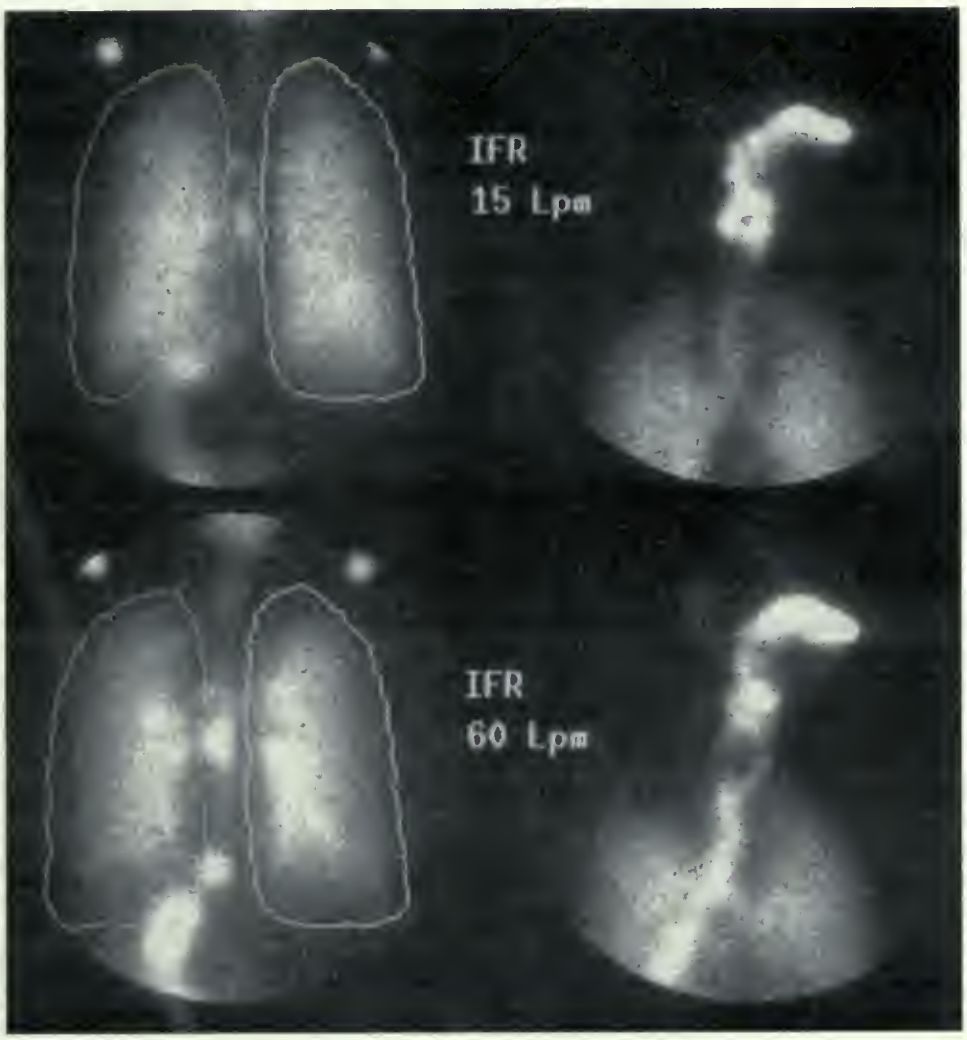

Fig. 7. Two-dimensional scan from a normal subject showing the distribution of ^{99m}technetium-DTPA albuterol sulphate powder inhaled at 15 L/m (upper row) and at 60 L/m (lower row) from the Spiros dry powder inhaler.[57] Deposition as a percent of the emitted dose was: lung 45.4% at 15 L/m and 36.3% at 60 L/m, oropharynx 19.6% at 15 L/m and 39.2% at 60 L/m. IFR = inspiratory flow rate.

on the IFR and particle size of the dispensed aerosol (Table 5 and Figure 6).[50,51] In addition, lung doses vary between infants, children, adults and geriatric patients, a function both of breathing pattern and oropharyngeal and airway geometry and, therefore, one might expect variable clinical response among various patient populations.[30, 51–53]

There is good evidence in the literature, particularly from a number of radiolabeled-particle deposition studies in normals and patients, confirming that peripheral lung deposition increases as inhaled aerosol particle size decreases and that central airway deposition increases with increased IFR and reduced airway caliber. What is less clear is whether utilizing therapeutic aerosols of specified size, inhaled at a specified flow to target specific receptor sites in the lung significantly influences clinical response. As mentioned above, several studies using targeted therapy have been described in the literature.[10–12] Improved response may be due to an increased total dose of drug deposited or to changing the site of deposition of the dose.

More recently, Zanen et al demonstrated, in a series of studies, significant improvement in forced expiratory volume in the first second response in patients inhaling 2.8 μm MMAD monodisperse aerosols of drug (salbutamol sulphate or ipratropium bromide or fenoterol), compared to their inhaling equal doses generated as 1.5 μm or 5.0 μm aerosols.[54,55] Though the dose of drug administered was estimated to be equivalent to that portion of a pMDI that contained respirable drug (drug contained in particles < 5 μm), it was not possible to show an improved response to the monodisperse aerosol, compared to the

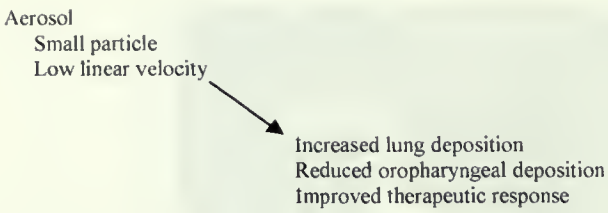

Fig. 8. Factors Promoting Successful Inhaled Therapy

pMDI.[56] However, if technological advances can produce devices that generate monodisperse aerosols, it may be possible to treat patients with lower doses of drug.

Radiolabelled-drug studies and clinical trials have demonstrated, in normals, asthmatics, and patients with chronic obstructive pulmonary disease, the benefit of inhaling pMDI aerosols at low IFRs. Reduced lung delivery and response has been shown to occur at IFRs exceeding 60 L/min, with increased distribution of the aerosol to the central airways and decreased distribution to the peripheral lung. The exception may be the inhalation of anticholinergic aerosols, since receptors for this class of drug are located more proximally in the lung. Figure 7 shows the effect of air flow on drug delivered. In this subject, the inhalation of a radiolabeled powder at 15 L/min produced much greater delivery to the lung and penetration of aerosol beyond the mid-lung region than inhalation at the higher air flow of 60 L/min.[57] Deposition is reduced at the high flow and is concentrated around the hilum, but is also more peripherally deposited with the lower IFR.

Nebulizers

Inhalation of aerosol from standard and/or breath-actuated nebulizer designs is typically performed at low IFRs, usually with tidal breathing. However, if the patient is hyperventilating, the same principles apply as for the other delivery systems: more drug will be deposited in the mouth and on central airways at high IFRs. The reduced duty cycle (ratio of inspiratory time to total breathing cycle time) translates into less drug inhaled. For crying infants and children, it is recommended that traditional nebulizer therapy be given when the child is quiet or asleep.

Recent developments in nebulizer design, in particular the metered-dose liquid inhaler,[58] may incorporate features that help control breathing factors during inhalation.[59]

Modelling In Vivo Delivery of Aerosol

Computerized breath simulators for assessing device performance are useful in estimating in vitro drug delivery to the mouth under various breathing conditions. The variables that can be tested with these systems are usually limited to tidal volume (10–1,000 mL) and inspiration-expiration ratio. Changes to either of these factors alters the peak IFR of the simulated breath pattern. Increased delivery of dose dispensed from pMDIs with valved spacers, as well as from jet nebulizers, has been measured with increasing tidal volume and increasing IFR.[60,61] However, as numerous studies have demonstrated, the fate of this inhaled aerosol (deposition and distribution in the lung) is additionally affected by the IFR. Capturing actual breath patterns from patients to feed into the simulator should improve the accuracy of these dose estimations. In addition, it should be accepted practice when modelling drug delivery to the lung that the particle size characteristics of the aerosol be determined under the various conditions of air flow. This would improve the accuracy in estimating lung dose and site of deposition, not only for optimal IFRs, but also for those situations where the inhalation technique is less than ideal.

Summary

A number of studies in the literature support the use of fine aerosols of drug, inhaled at low IFRs to target peripheral airways, with the objective of improving clinical responses to inhaled therapy (Fig. 8). Attempts have been made to separate response due to changes in total administered dose or the surface concentration of the dose from response due to changes in site of deposition—both are affected by the particle size of the aerosol, with IFR additionally influencing the latter.

The tools for measuring dose and distribution have improved over the last 10–15 years, and thus we should expect greater accuracy in these measurements for assessing drug delivery to the lung.[62] There are still issues, though, in producing radiolabeled ^{99m}technetium aerosols that are precise markers for the pharmaceutical product being tested and in quantitating absolute doses deposited in the lung. PET isotopes may provide the means for directly labelling a drug and perhaps can offer an alternative for making these measurements in the future, but deposition measurements should not be used in isolation; protocols should incorporate clinical tests to provide parallel therapeutic data in response to inhalation of the drug by the various patient populations being studied.

REFERENCES

1. Newman SP. Scintigraphic assessment of therapeutic aerosols. Crit Rev Ther Drug Carrier Syst 1993;10(1):65–109.
2. Dolovich M. Aerosols. In: Barnes PJ, Grunstein MM, Leff AR, Woolcock AJ, editors. Asthma. Philadelphia: Lippincott-Raven; 1997: 1349–1366.
3. Morrow PE, Yu CP. Models of aerosol behavior in airways and alveoli. In: Morén F, Dolovich MB, Newhouse MT, Newman SP, editors. Aerosols in medicine: principles, diagnosis and therapy, 2nd ed. Amsterdam: Elsevier; 1993: 157–193.

4. Auty RM, Brown K, Neale MG, Snashall PD. Respiratory tract deposition of sodium cromoglycate is highly dependent upon technique of inhalation using the Spinhaler. Br J Dis Chest 1987;81(4): 371–380.
5. Newnham DM, Lipworth BJ. Nebuliser performance, pharmacokinetics, airways and systemic effects of salbutamol given via a novel nebuliser delivery system ("Ventstream"). Thorax 1994;49(8):762–770.
6. Wilson AM, Dempsey OJ, Coutie WJ, Sims EJ, Lipworth BJ. Importance of drug-device interaction in determining systemic effects of inhaled corticosteroids (letter). Lancet 1999;353(9170):2128.
7. Lippmann M. Regional deposition of particles in the human respiratory tract. In: Lee DHK, Falk HL, Murphy SD, editors. Handbook of physiology, Section 9, Reaction to environmental agents. Bethesda MD: American Physiological Society; 1977: 213–232.
8. Chang HK, Menon AS. Airflow dynamics in the human airways. In: Morén F, Dolovich MB, Newhouse MT, Newman SP, editors. Aerosols in medicine: principles, diagnosis and therapy, 2nd ed. Amsterdam: Elsevier; 1993: 85–116.
9. Smaldone GC, Messina MS. Flow limitation, cough, and patterns of aerosol deposition in humans. J Appl Physiol 1985;59(2):515–520.
10. Ruffin RE, Dolovich MB, Wolff RK, Newhouse MT. The effects of preferential deposition of histamine in the human airway. Am Rev Respir Dis 1978;117(3):485–492.
11. Johnson MA, Newman SP, Bloom R, Talaee N, Clarke SW. Delivery of albuterol and ipratropium bromide from two nebulizer systems in chronic stable asthma: efficacy and pulmonary deposition. Chest 1989;96(1):6–10.
12. Dolovich M, Ryan G, Newhouse MT. Aerosol penetration into the lung: influence on airway responses. Chest 1981;80(6 Suppl):834–836.
13. Dickens GR, Wermeling DP, Matheny CJ, John W, Abramowitz W, Sista SM, et al. Flunisolide administered via metered dose inhaler with and without a spacer device and following oral administration (abstract). J Allergy Clin Immunol 1999; 103 (1 Pt 2): Abstract 504.
14. Lipworth BJ, Clark DJ. Lung delivery of salbutamol given by breath activated pressurized aerosol and dry powder inhaler devices. Pulm Pharmacol Ther 1997;10(4):211–214.
15. Chrystyn H. Anatomy and physiology in delivery: can we define our targets? Allergy 1999;54 Suppl 49:82–87.
16. Yu CP, Taulbee DB. A theory of predicting respiratory tract deposition of inhaled particles in man. Inhaled Part 1975;4 Pt 1:35–47.
17. Gerrity TR, Lee PS, Hass FJ, Marinelli A, Werner P, Lourenco RV. Calculated deposition of inhaled particles in the airway generations of normal subjects. J Appl Physiol 1979;47(4):867–873.
18. Gonda I. A semi-empirical model of aerosol deposition in the human respiratory tract for mouth inhalation. J Pharm Pharmacol 1981; 33(11):692–696.
19. Gonda I. Scintigraphic techniques for measuring in vivo deposition. J Aerosol Med 1996;9 Suppl 1:S59–S67.
20. Martonen TB, Yang Y, Dolovich M. Definition of airway composition within gamma camera images. J Thorac Imaging 1994;9(3): 188–197.
21. Phipps PR, Gonda I, Bailey DL, Borham P, Bautovich G, Anderson SD. Comparisons of planar and tomographic gamma scintigraphy to measure the penetration index of inhaled aerosols. Am Rev Respir Dis 1989;139(6):1516–1523.
22. Fleming JS, Hashish AH, Conway JH, Nassim MA, Holgate ST, Halson P, et al. Assessment of deposition of inhaled aerosol in the respiratory tract of man using three-dimensional multimodality imaging and mathematical modeling. J Aerosol Med 1996;9(3):317–327.
23. Rhodes CG, Hughes JMB. Pulmonary studies using positron emission tomography (review). Eur Respir J 1995;8(6):1001–1017.
24. Summers QA, Fleming JS, Dai Y, Perring S, Honeywell R, Gough KJ, et al. The pulmonary deposition of two aerosol preparations of nedocromil sodium delivered by MDI assessed by single photon emission computed tomography. J Aerosol Med 1996;9 Suppl 1:S93–S109.
25. Ojima F, Ido T, Takahashi T, Hatazawa J, Iro M, Sasaki H, et al. Preparation of a fine powder of 2-deoxy-2-[18F]fluoro-D-glucose suitable for inhalation to diagnose lung diseases by means of PET. Ann Nucl Med 1989;3(3):143–147.
26. Berridge MS, Heald DL. In vivo characterization of inhaled pharmaceuticals using quantitative positron emission tomography. J Clin Pharmacol 1999;Suppl:25S–29S.
27. Dolovich M, Nahmias C, Thompson M, Yuki S, Frietag A, Coates G. Positron emission tomographic (PET) imaging of the lung in cystic fibrosis: 3D assessment of the distribution of inhaled therapy (abstract). Am J Respir Crit Care Med 1999;159(4 Pt 2):A687.
28. Rahman S, Rhoades CG, Constantinou M, Waters S, Aigbirhio FI, Osman S, et al. Lung deposition of 18-F-fluticasone propionate in normal subjects using positron emission tomography therapy (abstract). Am J Respir Crit Care Med 2000;161(4 Pt 2):A177.
29. Dolovich MB, Sanchis J, Rossman C, Newhouse MT. Aerosol penetrance: a sensitive index of peripheral airways obstruction. J Appl Physiol 1976;40(3):468–471.
30. Dolovich M, Rushbrook J, Churchill E, Mazza M, Powles AC. Effect of continuous lateral rotational therapy on lung mucus transport in mechanically ventilated patients. J Crit Care 1998;13(3):119–125.
31. Ilowite JS, Gorvoy JD, Smaldone GC. Quantitative deposition of aerosolized gentamicin in cystic fibrosis. Am Rev Respir Dis 1987; 136(6):1445–1449.
32. Laube BL, Norman PS, Adams G 3rd. The effect of aerosol distribution on airway responsiveness to inhaled methacholine in patients with asthma. J Allergy Clin Immunol 1992;89(2):510–518.
33. Dolovich M, Nahmias C, Coates G. Unleashing the PET: 3D imaging of the lung. In: Byron P, Dalby R, Farr S, editors. Respiratory Drug Delivery VII. North Carolina: Serenta Publishers; (2000, in press).
34. Willeke K, Baron PA. Aerosol measurement: principles, techniques and applications. New York: Van Nostrand Reinhold; 1993.
35. Hallworth G. Particle size of therapeutic aerosols. In: Moren F, Dolovich M, Newhouse M, Newman S, editors. Aerosols in medicine: principles, diagnosis and therapy. Amsterdam: Elsevier; 1993: 351–374.
36. Meakin BJ, Ganderton D, Panza I, Ventura P. The effect of flow rate on drug delivery from the Pulvinal, a high- resistance dry powder inhaler. J Aerosol Med 1998;11(3):143–152.
37. Smith KJ, Chan HK, Brown KF. Influence of flow rate on aerosol particle size distributions from pressurized and breath-actuated inhalers. J Aerosol Med 1998;11(4):231–245.
38. Prime D, Grant AC, Slater AL, Woodhouse RN. A critical comparison of the dose delivery characteristics of four alternative inhalation devices delivering salbutamol: pressurized metered dose inhaler, Diskus inhaler, Diskhaler inhaler, and Turbuhaler inhaler. J Aerosol Med 1999;12(2):75–84.
39. Pedersen S, Hansen OR, Fuglsang G. Influence of inspiratory flow rate upon the effect of a Turbuhaler. Arch Dis Child 1990;65(3): 308–310.
40. Borgstrom L, Bondesson E, Moren F, Trofast E, Newman SP. Lung deposition of budesonide inhaled via Turbuhaler: a comparison with terbutaline sulphate in normal subjects. Eur Respir J 1994;7(1):69–73.
41. Borgstrom L, Derom E, Stahl E, Wahlin-Boll E, Pauwels R. The inhalation device influences lung deposition and bronchodilating effect of terbutaline. Am J Respir Crit Care Med 1996;153(5):1636–1640.

42. Devadason SG, Everard ML, MacEarlan C, Roller C, Summers QA, Swift P, et al. Lung deposition from the Turbuhaler in children with cystic fibrosis. Eur Respir J 1997;10(9):2023–2028.
43. Dolovich M. Lung dose, distribution and clinical response to therapeutic aerosols. Aerosol Sci Technol 1993;18:230–240.
44. Mitchell JP, Dolovich MB. A standard for testing of spacers and holding chambers: in vitro testing parameters (abstract). J Aerosol Med 1999;12(2):134.
45. Dolovich M, Rhem R. In vitro characterization of two BDP HFA pMDIs (abstract). J Aerosol Med 1999;12(2):112.
46. Dolovich M, Rhem R. In vitro comparison of a BDP HFA pMDI with CFC Beclovent®. Eur Respir J 1999:14(Suppl 30):197S, P1364.
47. Leach CL, Davidson PJ, Boudreau RJ. Improved airway targeting with the CFC-free HFA-beclomethasone metered-dose inhaler compared with CFC- beclomethasone. Eur Respir J 1998;12(6):1346–1353.
48. Dolovich MB, Rhem R, Gerrard L, Coates G. Lung deposition of coarse CFC vs fine HFA pMDI aerosols of beclomethasone dipropionate (BDP) in asthma (abstract). Am J Respir Crit Care Med 2000;161 (4 Pt2):A62.
49. Busse WW, Brazinsky S, Jacobson K, Stricker W, Schmitt K, Vanden Burgt J, et al. Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. J Allergy Clin Immunol 1999;104(6): 1215–1222.
50. Dolovich M, Ruffin RE, Roberts R, Newhouse MT. Optimal delivery of aerosols from metered dose inhalers. Chest 1981;80(6 Suppl): 911–915.
51. Thorsson L, Kenyon C, Newman SP, Borgstrom L. Lung deposition of budesonide in asthmatics: a comparison of different formulations. Int J Pharm 1998;168:119–121.
52. Fok TF, Monkman S, Dolovich M, Gray S, Coates G, Paes B, et al. Efficiency of aerosol medication delivery from a metered dose inhaler versus jet nebulizer in infants with bronchopulmonary dysplasia. Pediatr Pulmonol 1996;21(5):301–309.
53. Bisgaard H. Delivery of inhaled medication to children (review). J Asthma 1997;34(6):443–467.
54. Zanen P, Go LT, Lammers J-WJ. The optimal particle size for parasympathicolytic aerosols in mild asthmatics. Int J Pharm 1995;114(1): 111–115.
55. Zanen P, Go LT, Lammers JW. Optimal particle size for beta 2 agonist and anticholinergic aerosols in patients with severe airflow obstruction. Thorax 1996;51(10):977–980.
56. Zanen P, Go LT, Lammers JW. The efficacy of a low-dose, monodisperse parasympathicolytic aerosol compared with a standard aerosol from a metered-dose inhaler. Eur J Clin Pharmacol 1998;54(1): 27–30.
57. Dolovich M, Rhem R, Rashid F, Bowen B, Coates G, Hill M. Lung deposition of albuterol sulphate from the Dura Dryhaler on normal adults (abstract). Am J Respir Crit Care Med 1996;153(4 Pt 2):A62.
58. Dolovich M. New propellant-free technologies under investigation (review). J Aerosol Med 1999;12 Suppl 1:S9–S17.
59. Schuster J, Rubsamen R, Lloyd P, Lloyd J. The AERX aerosol delivery system. Pharm Res 1997;14(3):354–357.
60. Janssens HM, Krigsman AM, Verbraak AFM, Hop WCJ, de Jongste JC, Tiddens HAWM. Fine particle size improves lung deposition of inhaled steroids in infants: a study in an upper airway model (abstract). Am J Respir Crit Care Med 2000;161(4 Pt 2):A32.
61. Dolovich M, Rhem R, Kwong J. Simulating aerosol delivery: effect of particle size, tidal volume and inspiratory flow rate (abstract). Am J Respir Crit Care Med 1999;59(4 Pt 2):A615.
62. Everard M, Dolovich M. In vivo measurements of lung dose. In: Bisgaard H, O'Callaghan C, Smaldone G, editors. Lung biology in health and disease series New York: Marcel Dekker; (in press, 2000).

Nebulizers: Principles and Performance

Dean R Hess PhD RRT FAARC

Introduction
Pneumatic Nebulizers
Principle of Operation
Clinically Important Characteristics of Nebulizer Performance
Technical Factors Affecting Nebulizer Performance
Patient Factors Affecting Nebulizer Performance
Designs to Enhance Nebulizer Performance
Use of Reservoir Bags to Collect Aerosol During the Expiratory Phase
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Ultrasonic Nebulizers
Summary
[Respir Care 2000;45(6):609–622] *Key words: nebulizer, pneumatic nebulizer, ultrasonic nebulizer, continuous nebulization, aerosol therapy.*

Introduction

Nebulizers are used to convert liquids into aerosols of a size that can be inhaled into the lower respiratory tract. The process of pneumatically converting a bulk liquid into small droplets is called atomization. Pneumatic nebulizers have baffles incorporated into their design so that most of the droplets delivered to the patient are within the respirable size range of 1–5 μm. Ultrasonic nebulizers use electricity to convert a liquid into respirable droplets.

Although the first choice of aerosol generator for the delivery of bronchodilators and steroids is the metered-dose inhaler,[1,2] nebulizers remain useful for several reasons. First, some drugs for inhalation are available only in solution form. Second, some patients cannot master the correct use of metered-dose inhalers or dry powder inhalers. Third, some patients prefer the nebulizer over other aerosol generating devices. The physiologic benefits of metered-dose inhalers and nebulizers are virtually equivalent,[3,4] and the choice of device is often based on clinician or patient preference rather than clear superiority of one approach over the other. Although cost savings have been suggested with the use of metered-dose inhalers compared to nebulizers, these benefits may be overestimated.[3]

The purpose of this paper is to review the performance characteristics of nebulizers. Both pneumatic and ultrasonic nebulizer designs will be considered.

Pneumatic Nebulizers

Nebulizers are the oldest form of aerosol generation. Although they have been commonly used for many years, their basic design and performance has changed little over the past 25 years. Nebulizers are most commonly used for bronchodilator administration, and it is well established that nebulized bronchodilators produce a physiologic response. Because bronchodilators are relatively inexpensive, there is little market pressure to improve nebulizer performance. In fact, the market generally prefers an inexpensive nebulizer rather than a high-performance neb-

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Table 1. Factors Affecting Penetration and Deposition of Therapeutic Aerosols Delivered via Jet Nebulizer

Technical Factors
Manufacturer of nebulizer
Gas flow used to power nebulizer
Fill volume of nebulizer
Solution characteristics
Composition of the driving gas
Designs to enhance nebulizer output
Continuous versus breath-actuated
Patient Factors
Breathing pattern
Nose versus mouth breathing
Composition of inspired gas
Airway obstruction
Positive pressure delivery
Artificial airway and mechanical ventilation

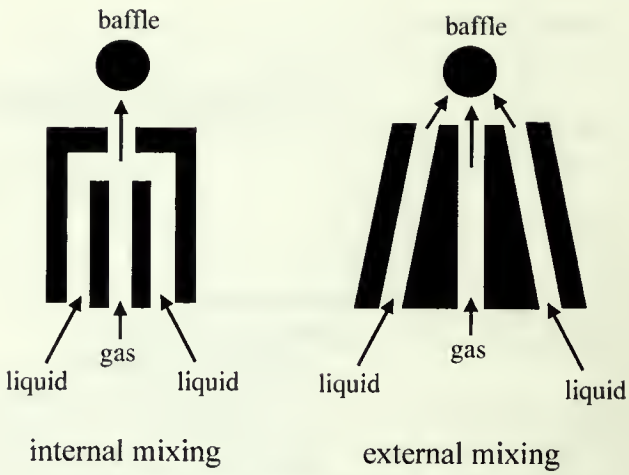

Fig. 2. Internal mixing and external mixing nebulizer designs. (Adapted from Reference 5.)

ulizer for bronchodilator administration. However, there are newer drugs available for inhalation that are expensive and for which precise dosing may be important. These include dornase alfa, tobramycin, and pentamidine. Nebulizer performance is affected by both technical and patient-related factors (Table 1).

Principle of Operation

The operation of a pneumatic nebulizer requires a pressurized gas supply as the driving force for liquid atomization (Fig. 1).[5–10] Compressed gas is delivered through a jet, causing a region of negative pressure. The solution to be aerosolized is entrained into the gas stream and is sheared into a liquid film. This film is unstable and breaks into droplets because of surface tension forces. A baffle is placed in the aerosol stream, producing smaller particles and causing larger particles to return to the liquid reservoir. More than 99% of the particles may be returned to the liquid reservoir.[8] The aerosol is delivered into the inspiratory gas stream of the patient. Before delivery into the patient's respiratory tract, the aerosol can be further conditioned by environmental factors such as the relative humidity of the carrier gas.[11–14]

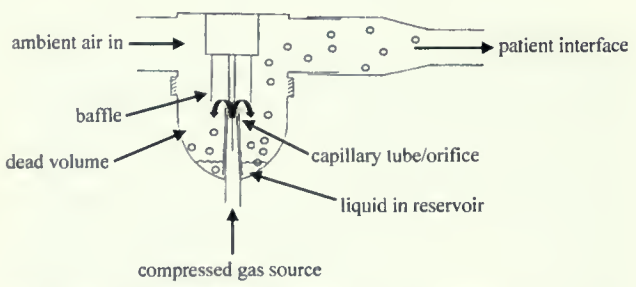

Fig. 1. Basic components of the design of pneumatic nebulizers. (Adapted from Reference 6.)

Nebulizer nozzles are of two types (Fig. 2).[15] With the internal mixing design, gas flow interacts with the solution prior to leaving the exit port. With external mixing, gas and the solution interact after both leave the nozzle. Modifications on these designs are used by nebulizer manufacturers, without clear superiority of one approach over the other.

Determinants of droplet size produced by nebulizers include the characteristics of the solution (density, viscosity, surface tension), the velocities of the gas and solution, and the flow rates for the gas and the solution.[5,15] The most important factors are gas velocity and the ratio of liquid to gas flow.[5] An increase in gas velocity decreases droplet size, whereas an increase in the ratio of liquid to gas flow increases particle size. It is interesting to note that gas velocity affects the flow rates for both the gas and the solution. Thus, it is impossible to separately control the primary factors affecting droplet size from nebulizers.

An important consideration in the use of nebulizers is the dead volume of the device. Dead volume refers to the amount of solution that is trapped inside the nebulizer and is thus not made available for inhalation. The dead volume is typically in the range of 1 to 3 mL. Dead volume is minimized by using a conical shape of the nebulizer, by decreasing the surface area of the internal surface of the nebulizer, and by improving the wetness of the plastic surface of the nebulizer.[5,15] To reduce medication loss due to dead volume, clinicians and patients may tap the nebulizer periodically during therapy, which has been shown to increase nebulizer output.[16] Therapy may also be continued past the point of inconsistent nebulization (sputtering) in an attempt to deliver medication from the dead volume, but this has been reported to be unproductive.[17]

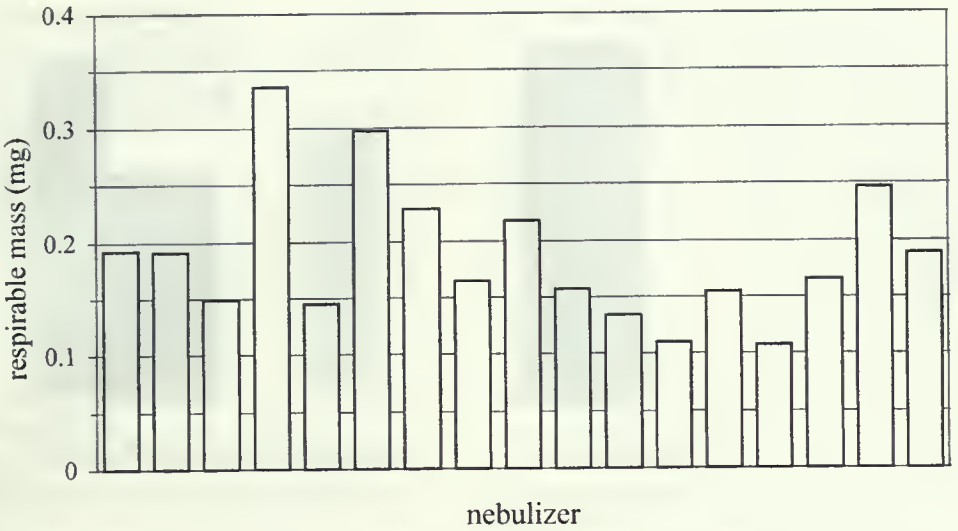

Fig. 3. Comparison of the output of 17 commercially available pneumatic nebulizers. Respirable mass = particles 1–5 μm delivered to mouthpiece with simulated spontaneous breathing; 2.5 mg albuterol placed into nebulizer cup. (Adapted from Reference 25.)

Due to evaporative water loss, the solution in the nebulizer becomes increasingly concentrated during the nebulization time.[18–20] For this reason, gravimetric methods underestimate nebulizer output.[21,22] Due to the evaporative effects, the nebulizer solution cools.[18] Solution temperature affects nebulizer output, with output varying directly with temperature.[15,23] The droplet size produced by the nebulizer also varies directly with temperature.[18]

Clinically Important Characteristics of Nebulizer Performance

The most important characteristic of nebulizer performance is the respirable dose provided for the patient. The respirable dose is determined by the mass output of the nebulizer and the size of the droplets that are produced. The droplet size should be 2–5 μm for airway deposition and 1–2 μm for parenchymal deposition.[24] Droplet size is usually reported as mass median aerodynamic diameter (MMAD), which is the diameter around which the mass of the aerosol is equally divided. Note that MMAD is used to characterize the population of droplets produced; it does not refer to the size of individual droplets. Because the volume, and hence the mass, of the droplet is determined by the cube of the radius (volume = $4/3\ \pi r^3$), most of the particles will be smaller than the MMAD. The respirable dose is sometimes reported as respirable mass, which is the output of droplets from a nebulizer in the respirable range of 1–5 μm.[25,26]

Other important characteristics of nebulizer performance include nebulization time, cost, ease of use, and requirements for cleaning and sterilization. Nebulization time is important for patient compliance in the outpatient setting and clinician supervision for hospitalized patients. A short nebulization time that delivers an effective dose is desirable. Many nebulizers are low-cost, mass-produced, single-patient-use devices. This results in variability in performance among devices,[25–28] which might not be important for bronchodilator delivery, but which could be important for delivery of other inhaled medications.

Technical Factors Affecting Nebulizer Performance

Several studies have reported performance differences between nebulizers from different manufacturers.[23,25–27,29–36] Performance differences among nebulizers from the same manufacturer have been reported.[37–39] Hess et al[25] evaluated the performance of 17 nebulizers, using a model of spontaneous breathing. They reported a respirable mass available to the patient that was severalfold greater from some nebulizers than from others (Fig. 3). Performance differences between nebulizers may have clinical implications.[37,40–43] In healthy subjects, Hardy et al[42] reported aerosol deposition from some pneumatic nebulizers that was twice that of others. In subjects with chronic stable asthma, Johnson et al[43] reported differences in bronchodilation between nebulizers from different manufacturers.

Because of cost considerations, disposable single-patient-use nebulizers are typically used for many treatments. The effects of repetitive use and cleaning were evaluated by Standaert et al.[44] In that study, nebulizers were found to function correctly for 100 repeated uses, provided they were properly maintained. Proper maintenance consisted of washing with soapy water, rinsing, and air drying after each use. Each nebulizer was also subjected to a daily 30-minute soak in 2.5% acetic acid. In the same study,[44] it

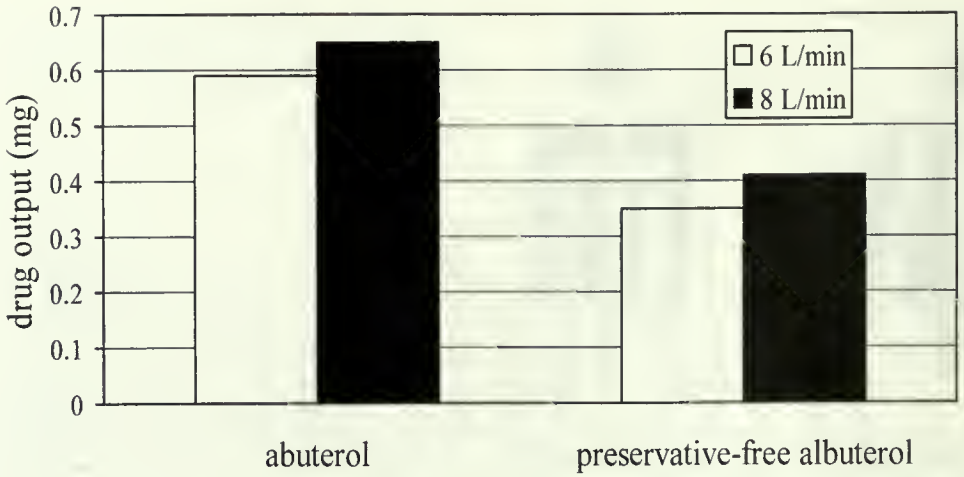

Fig. 4. Comparison of albuterol output of a pneumatic nebulizer, using two formulations of albuterol. (Drawn from data in Reference 38.)

was reported that the nebulizers started to fail after 40 uses if they were not cleaned after each use.

Several studies have reported greater output from pneumatic nebulizers when the fill volume is increased.[23,25,33,34,45] This is probably because nebulizers have a fixed dead volume, and thus an increase in fill volume reduces the proportion of dead volume within the nebulizer. Although nebulizer output increases with a greater fill volume, there is also an increase in nebulization time.[25] The nebulization time can be reduced when a larger fill volume is used by increasing the flow to power the nebulizer.[23,25] A nebulizer fill volume of 4–5 mL is recommended.

Output increases with an increased flow to power the nebulizer.[23,25,33] An increase in flow also decreases the droplet size produced by nebulizers.[25,39,46–48] A flow of 8 L/min is recommended. Flows lower than this result in decreased nebulizer performance. A flow greater than this may result in increased drug loss during the expiratory phase, which offsets the effect of greater flow on nebulizer output.[25]

It is not commonly appreciated that the drug formulation can affect nebulizer performance. MacNeish et al[38] reported differences in nebulizer output with two formulations of albuterol. Nebulizer output was significantly greater with the formulation containing the preservative benzalkonium chloride, probably because of its surface activity (Fig. 4). Large droplets were seen to adhere to the walls of the nebulizer with the preservative-free formulation, whereas foaming was seen to occur with the preservative-containing formulation. Others have also reported effects of drug formulation on nebulizer output.[39,49] It is interesting to note that metered-dose inhalers have always been tested and approved as a drug-delivery-system combination. Newer drug solutions have also been approved for a specific nebulizer (eg, pentamidine, ribavirin, dornase alpha, tobramycin).

The density of the gas powering the nebulizer affects nebulizer performance. Hess et al[50] reported the effect of heliox (80% helium, 20% oxygen) on nebulizer function. The inhaled mass of albuterol was significantly reduced when the nebulizer was powered with heliox, and there was a greater than twofold increase in nebulization time with heliox. An increased flow with heliox produced a respirable mass output similar to that produced when the nebulizer was powered with air. These results are explained by Bernoulli's principle, which predicts that the decreased density of heliox increases the velocity at which the gas leaves the jet orifice and produces less negative pressure to entrain drug solution.[50]

Patient Factors Affecting Nebulizer Performance

The breathing pattern of the patient affects the amount of aerosol deposited in the lower respiratory tract. This partially explains differences in aerosol deposition between children and adults. To improve aerosol penetration and deposition in the lungs, the patient should be encouraged to use a slow and deep breathing pattern.[51] Because of the effect of breathing pattern on drug delivery from nebulizers, in vitro evaluations of nebulizer performance should be conducted in a manner that simulates the breathing pattern of a patient.[52]

Inhaled aerosols can be administered using a mouthpiece or a face mask.[53–57] Bronchodilator responses occur with both techniques, and some have argued that the selection of interface should be based on patient preference.[53] However, it should be appreciated that the nasal passages effectively filter droplets delivered from the nebulizer. Everard et al[54] reported a nearly 50% reduction in aerosol

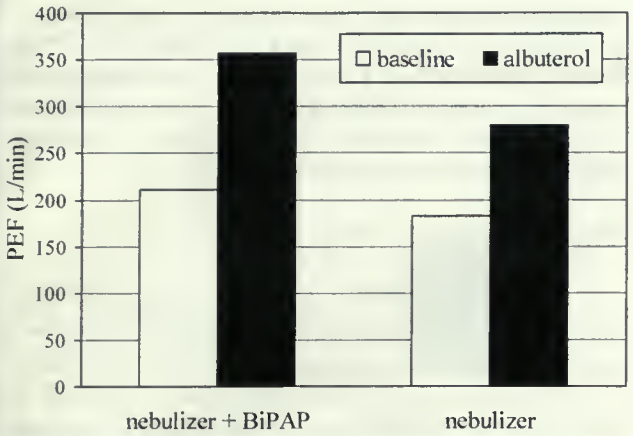

Fig. 5. Peak expiratory flow (PEF) responses with albuterol delivery by nebulizer with bilevel positive airway pressure (BiPAP) or by nebulizer alone. (Drawn from data in Reference 68.)

delivery to the lungs with nasal inhalation. Whether a mouthpiece or a face mask is used, it is important to instruct the patient to inhale through the mouth. Use of a mouthpiece may encourage oral breathing.[54] It is interesting to note that asthmatic patients switch their breathing route from the nasal route to the oronasal route during acute exacerbations and, even when not acutely bronchoconstricted, switch to oronasal breathing when wearing a face mask.[58]

Airway caliber affects lung delivery of nebulized bronchodilators.[59–61] Lipworth et al[61] reported lower plasma albuterol concentrations and attenuated bronchodilator responses in patients with severe asthma than in normal subjects or those with mild asthma. It is ironic that the air flow obstruction that produces the need for inhaled bronchodilator therapy also decreases the effectiveness of that therapy.

Several studies have reported greater pulmonary penetration of aerosols in patients with stable asthma and with acute airway constriction during heliox breathing.[62–66] Because of the lower density and greater viscosity of heliox, gas flow becomes less turbulent, which theoretically improves the transport of aerosols through constricted airways to more peripheral lung regions. Henderson et al[67] reported no significant advantage of heliox-driven nebulizer therapy over oxygen-driven nebulizer therapy. However, they[67] did not account for the effect of heliox on nebulizer function,[50] and this may have contributed to their negative findings.

Nebulizer therapy has been used in combination with noninvasive ventilation. Pollack et al[68] randomized patients with acute asthma to receive either bronchodilator therapy with a nebulizer and face mask or with a nebulizer, nasal mask, and BiPAP (bi-level positive airway pressure system made by Respironics). The BiPAP settings were: inspiratory pressure 10 cm H_2O, expiratory pressure 5 cm H_2O. The patients who received bronchodilator therapy with BiPAP had a greater improvement in peak flow (Fig. 5). Although these results are intriguing, further positive reports are needed before widespread acceptance of this practice. Interestingly, this approach to nebulizer therapy is reminiscent of intermittent positive-pressure breathing, which was abandoned many years ago as a method for delivery of inhaled bronchodilators to patients with asthma.

Nebulizer therapy is commonly used in mechanically ventilated patients, and this topic has been reviewed in detail elsewhere.[69–73] A number of factors are known to affect aerosol delivery from nebulizers during mechanical ventilation (Table 2).[12] There are disadvantages of nebulizer use during mechanical ventilation, such as circuit contamination,[74] decreased ability of the patient to trigger the ventilator[75] (if the nebulizer is not powered by the ventilator), and increases in the delivered tidal volume and airway pressure[76] (if the nebulizer is not powered by the ventilator). The nebulizer is less efficient than the metered-dose inhaler during mechanical ventilation, but the nebulizer delivers a greater dose to the lower respiratory tract.[77]

Designs to Enhance Nebulizer Performance

In recent years, several nebulizer designs have become available to decrease the amount of aerosol lost during the expiratory phase.[78] These include reservoir bags to collect aerosol during the expiratory phase, the use of a vented design to increase the nebulizer output during the inspiratory phase (breath-enhanced nebulizers), and nebulizers that only generate aerosol during the inspiratory phase (breath-actuated nebulizers). Because these designs improve drug delivery to the patient, they have the potential to reduce treatment time, which should improve patient compliance with nebulizer therapy.

Use of Reservoir Bags to Collect Aerosol During the Expiratory Phase

For many years, it has been a common practice to use a T-piece and corrugated tubing as a reservoir for small-

Table 2. Factors Affecting Aerosol Delivery from Nebulizers During Mechanical Ventilation

Endotracheal tube size
Position of nebulizer placement in the circuit
Type of nebulizer and fill volume
Humidification of the inspired gas
Treatment time
Duty cycle (I:E ratio)
Ventilator brand

I:E ratio = ratio of inspiratory time to expiratory time.

Fig. 6. Two designs of nebulizer device that use a reservoir bag. Circulaire (left) and AeroTee (right).

volume nebulizers.[79] In the late 1980s and early 1990s, there were reports of increased aerosol delivery to the lower respiratory tract when a plastic chamber was used with the nebulizer to capture aerosol during the expiratory phase, and provide that to the patient during the subsequent inspiration.[80,81] In the United States, a similar concept was incorporated into the Circulaire and AeroTee designs (Fig. 6). Both of these designs use a 750 mL bag to store aerosol during exhalation, but differ in how they prevent rebreathing. The Circulaire uses a one-way valve to prevent exhaled gas from entering the reservoir bag, whereas the AeroTee allows some exhaled gas to enter the bag.[82] These designs also decrease environmental contamination with the aerosol that is generated. The Circulaire incorporates a variable inspiratory/expiratory resister that is set to maximize inspiration from the reservoir bag, and to provide a positive expiratory pressure effect.

Mason et al[83] reported an MMAD of 0.51 μm with the Circulaire. Compared with a conventional nebulizer, they also reported better lung deposition, less gastrointestinal deposition, and less drug loss to the environment (Fig. 7). However, there are several important observations about these results. First, of 9 normal subjects, 2 actually had decreased pulmonary deposition with the Circulaire. This illustrates why caution must be exercised when applying group data to individual patients. Second, the conventional nebulizer used by Mason et al[83] does not perform as well as the nebulizer incorporated into the Circulaire. Thus, it is unclear whether the results were the effect of the reservoir bag or the nebulizer. The MMAD reported by Mason et al[83] for the Circulaire is not ideal. For maximal pulmonary deposition of bronchodilators, an MMAD of 1–5 μm is more desirable.

In another study by Mason et al,[84] the Circulaire was compared to a conventional nebulizer for bronchodilator delivery in patients with chronic obstructive pulmonary disease. In that study, the pulmonary deposition and therapeutic effect were similar for the Circulaire and the conventional nebulizer. Hoffman et al[85] compared the Circulaire to a conventional nebulizer for bronchodilator delivery in patients with acute bronchospasm presenting to an emergency department. They reported a greater improvement in bronchospasm (measured by peak flow) in the Circulaire group. In this study,[85] like those by Mason et al,[83,84] the nebulizer used with the Circulaire may have been superior to the conventional nebulizer that was used and, thus, the study may have compared the performance of nebulizers rather than the effect of the reservoir bag.

Breath-Enhanced Nebulizers

The traditional nebulizer design incorporates the nebulizer sidestream to the air flow of the patient. Some newer nebulizers use a mainstream design with valves. In this valved open-vent design, the patient breathes through the nebulizer during inspiration, which enhances the nebulizer output. During the expiratory phase, a one-way valve directs patient flow away from the nebulizer chamber (Fig. 8).

This design has been evaluated in several studies, which have reported greater pulmonary deposition with this design than with a conventional nebulizer.[86–88] A potential advantage of the open-vent nebulizer design is an improvement in nebulizer output with an increase in inspiratory flow. Coates et al[31] reported a greater output of tobramycin with increased inspiratory flow, using an open-vent nebulizer, whereas changes in inspiratory flow did not affect the output of the conventional nebulizer (Fig. 9). As with conventional nebulizers, performance differences between breath-enhanced nebulizers have been reported.[88,89]

Breath-Actuated Nebulizers

Aerosol waste during the expiratory phase can be eliminated if the nebulizer is only active during the inspiratory phase. Methods to manually actuate the nebulizer during the inspiratory phase have been available for many years.[45,90] It is also of interest to note that this design is commonly used in mechanical ventilator-actuated designs.[91,92] Both pneumatically and electronically controlled breath-actuated nebulizers have recently become commercially available. Their role in clinical application is yet to be determined.

Continuous Nebulization

Since the late 1980s, there has been considerable clinical and academic interest in the use of continuous aerosolized bronchodilators for the treatment of acute asthma[93–106] (Table 3). These studies suggest that this therapy is safe, at least as effective as intermittent nebulization, and may be superior to intermittent nebulization in patients with the most severe pulmonary function.

Several configurations have been described for continuous nebulization.[107] These include frequent refilling of

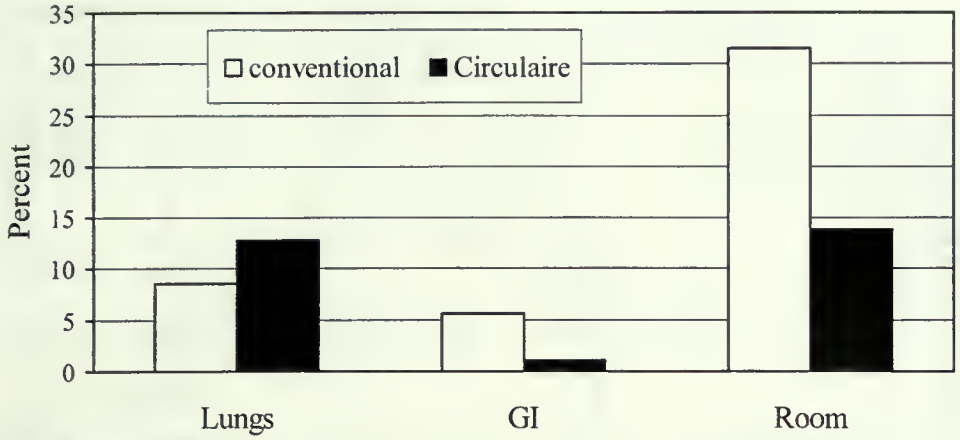

Fig. 7. Percent of drug delivery to the lungs, gastrointestinal (GI) tract, and room using a Circulaire nebulizer system. (Drawn from data in Reference 83.)

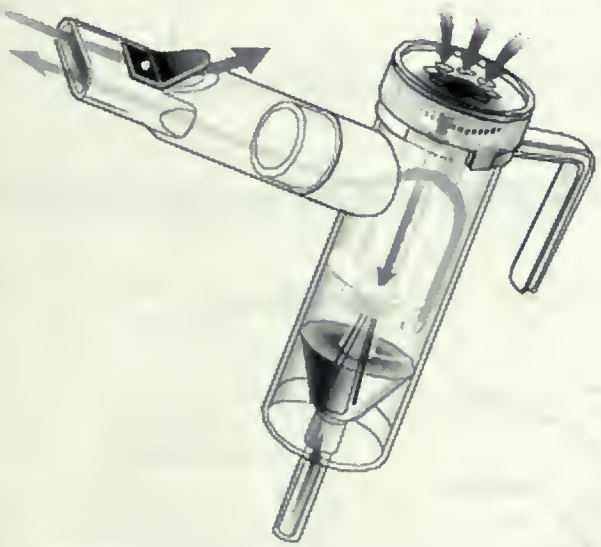

Fig. 8. Schematic representation of the function of a breath-enhanced nebulizer. Courtesy of Pari Respiratory Equipment.

the nebulizer,[93,101,104,106] use of a nebulizer and infusion pump (Fig. 10),[94,96,99,102,103,108] and use of a large-volume nebulizer.[95,97,98,106,109] Berlinski et al[110] reported a consistent and adequate aerosol production by a large-volume nebulizer over a 4-hour period of operation. Reisner et al,[111] however, reported a more consistent aerosol delivery with a small-volume nebulizer attached to an infusion pump than with a large-volume nebulizer. A commonly used large-volume nebulizer for this therapy is the High-output Extended Aerosol Respiratory Therapy (HEART) nebulizer. Raabe et al[112] reported a detailed evaluation of the performance of the HEART nebulizer. At a flow of 10–15 L/min, the aerosol output was 38–50 μL of aerosolized drug per liter of gas flow, and the solution output was 30–56 mL/hr.

McPeck et al[113] compared the HEART nebulizer to a conventional small-volume nebulizer in a model of adult and pediatric breathing. With the adult breathing pattern they reported similar aerosol delivery from the HEART nebulizer and small-volume nebulizer. For the pediatric breathing pattern the aerosol delivery from the small-volume nebulizer was greater than from the HEART. Both Raabe et al[112] and McPeck et al[113] reported an MMAD of about 2 μm with the HEART nebulizer. An important finding of McPeck et al[113] was that the albuterol delivery from the HEART nebulizer was significantly less than the target dose from the manufacturer's recommended setup.

Nebulizers for Specific Applications

Specially constructed small-volume nebulizers should be used when contamination of the ambient environment with the aerosolized drug needs to be avoided.[35,114,115] The most common example is aerosolized pentamidine.[116] The nebulizer is fitted with one-way valves and filters to prevent gross contamination of the environment. Examples of these devices include the Cadema Aero-Tech II and the Respirgard II. These devices produce a very small particle size, with an MMAD of about 1–2 μm, which is necessary to improve alveolar deposition of the drug.

The Small-Particle Aerosol Generator is used specifically to aerosolize ribavirin (Virazole).[117–119] The device consists of a nebulizer and a drying chamber. The drying chamber reduces the MMAD of particles to about 1.3 μm. There are concerns about the potential adverse effects of this drug on health care workers when ribavirin is used. For this reason, a scavenging system should be used when ribavirin is administered.[120–122] This is a double-enclosure system, with a ribavirin administration hood or mask inside a tent. Two high-flow vacuum scavenging systems

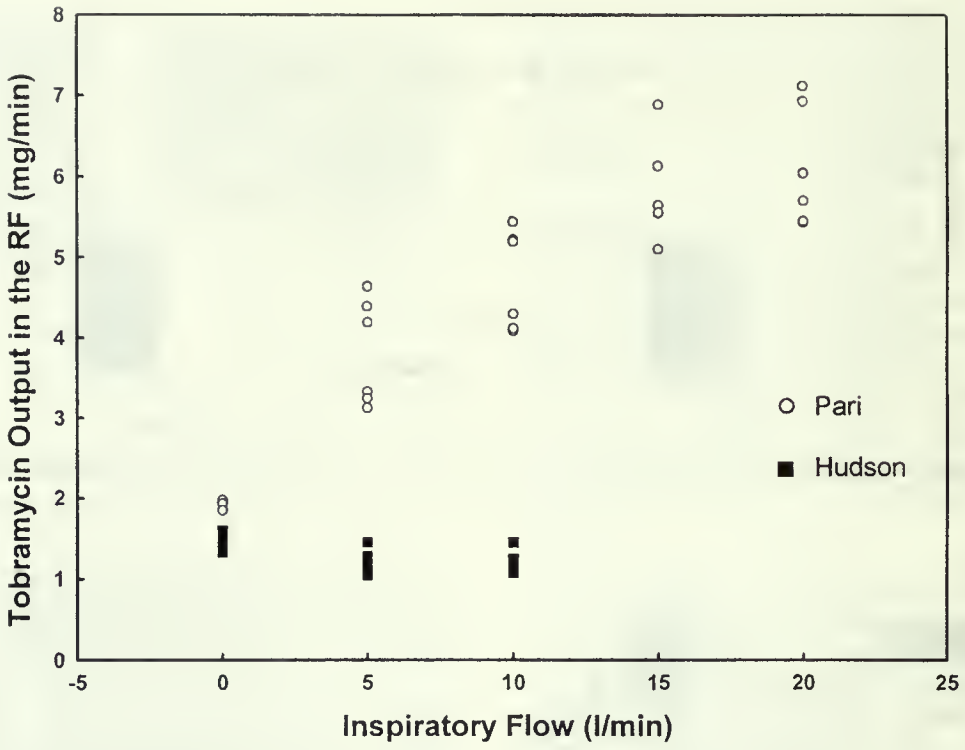

Fig. 9. Tobramycin output from a conventional nebulizer (Hudson) and a breath-enhanced nebulizer (Pari) with changes in inspiratory flow. RF = respirable fraction. (From Reference 31, with permission.)

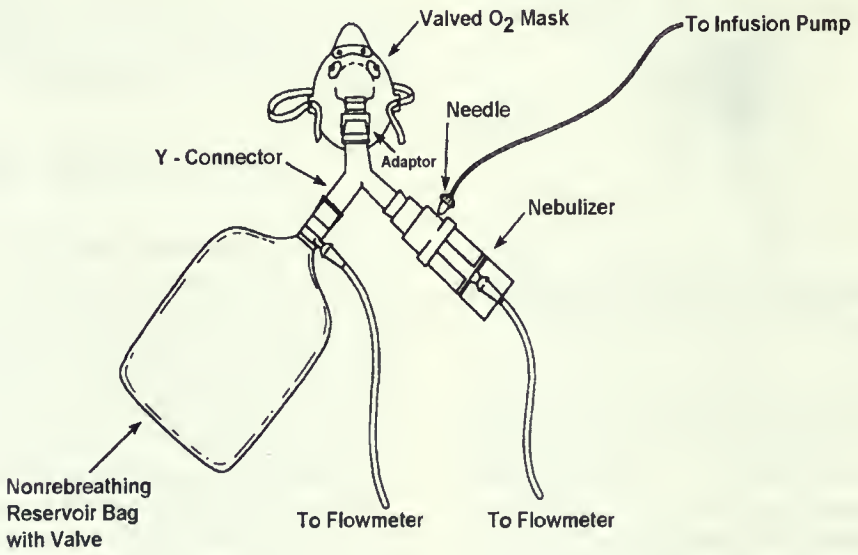

Fig. 10. System for continuous bronchodilator administration using a conventional nebulizer and an infusion pump. (From Reference 103, with permission.)

aspirate ribavirin from the system through high-efficiency particulate air filters.

Ultrasonic Nebulizers

Ultrasonic nebulizers have been clinically available since the 1960s.[123,124] Small-volume ultrasonic nebulizers are commercially available for delivery of inhaled bronchodilators.[125–131] Although several studies reported greater bronchodilator response with ultrasonic nebulizers than with other aerosol generators,[127,128] this has not been confirmed in other studies.[129–131] Large-volume ultrasonic nebulizers are used to deliver inhaled antibiotics in patients with cys-

Table 3. Summary of Studies Reporting Use of Continuous Nebulization

Author	Study Population	Drug	Research Design	Continuous Nebulizer Design	Major Finding
Portnoy[93]	Children with severe asthma	Terbutaline; 1–12 mg/h	Case series	Frequent refilling of conventional nebulizer	Continuously nebulized terbutaline safe and effective for treatment of severe asthma.
Moler[103]	Children with severe asthma	Terbutaline; 4 mg/h	Case series	Conventional nebulizer with infusion pump	Continuously nebulized terbutaline is an effective therapy for severe asthma.
Calcacone[95]	Adults with acute asthma	Albuterol; 10 mg over 2 h	Randomized controlled trial	Large volume nebulizer	Continuous nebulization was as effective as intermittent nebulization.
Chipps[109]	Children with bronchospasm	Terbutaline; 4 mg/h	Case series	HEART nebulizer	18 of 23 cases showed significant improvement with continuous nebulization.
Papo[96]	Children with status asthma	Albuterol; 0.3 mg/kg/h	Randomized controlled trial	Conventional nebulizer with infusion pump	Continuous nebulization was safe and resulted in more rapid improvement than intermittent nebulization.
Lin[97]	Adults with acute asthma	Albuterol; 30 mg over 110 min	Randomized controlled trial	HEART nebulizer	Continuous nebulization most beneficial in patients with $FEV_1 < 50\%$ predicted.
Rudnitsky[98]	Adults with acute asthma	Albuterol; 10 mg over 70 min	Randomized controlled trial	HEART nebulizer	Continuous nebulization may be of benefit for patients with peak flow < 200 L/min.
Lin[99]	Adults with acute asthma	Albuterol; 0.4 mg/kg/h for 4 h	Case series	Conventional nebulizer with infusion pump	High dose continuous nebulization can result in markedly elevated serum albuterol levels and potential cardiac stimulation.
Katz[100]	Infants and children with bronchospasm	Albuterol; 3 mg/kg/h	Case series	Not reported	Continuous albuterol safe and without significant evidence of cardiotoxicity.
Olshaker[101]	Adults with acute asthma	Albuterol; 7.5 mg over 1 h	Case series	Frequent refilling of conventional nebulizer	Continuous nebulization was safe and effective.
Baker[105]	Adults with acute asthma	Albuterol; 10 mg/h	Retrospective case control	Conventional nebulizer with infusion pump	Continuous and intermittent nebulization were similar in terms of safety, morbidity, and mortality.
Reisner[111]	Adults with acute asthma	Albuterol; 7.5 mg/h	Randomized controlled trial	Conventional nebulizer with infusion pump	Continuous nebulization was as safe and effective as intermittent nebulization.
Moler[103]	Children with acute asthma	Terbutaline; 16 mg over 8 h	Randomized controlled trial	Conventional nebulizer with infusion pump	Continuous nebulization produced similar plasma terbutaline levels and cardiovascular effects as intermittent nebulization.
Shrestha[104]	Adults with acute asthma	Albuterol; 2.5 mg or 7.5 mg over 2 h	Randomized controlled trial	Frequent refilling of conventional nebulizer	The standard dose continuous nebulization group had the greatest improvement with the fewest side effects.
Weber[106]	Adults with acute asthma	Albuterol at 10 mg/h; ipratropium at 1 mg/h	Randomized controlled trial	HEART nebulizer	There was no significant difference in outcomes for patients receiving continuous albuterol alone or continuous albuterol with ipratropium.

Table 4. Advantages and Disadvantages of Ultrasonic Nebulizers

Advantages
Little patient coordination required
Small dead volume
Quiet
Aerosol accumulates during exhalation
High doses possible
No chlorofluorocarbon release
Fast drug delivery
Disadvantages
Expensive
Contamination possible
Prone to electrical and mechanical breakdown
Not all drug formulations available
Drug preparation required

tic fibrosis (eg, tobramycin).[132–135] Ultrasonic nebulizers have also been used during mechanical ventilation,[136–139] where they have an advantage in that they do not augment tidal volume, as occurs with pneumatic nebulizers.

Table 4 lists advantages and disadvantages of ultrasonic nebulizers for medication delivery. Table 5 lists factors affecting output from ultrasonic nebulizers.[140] A potential issue with the use of ultrasonic nebulizers is the possibility of drug inactivation by the ultrasonic waves,[141] although this has not been shown to occur with commonly-used nebulized medications.

The ultrasonic nebulizer uses a piezoelectric transducer to produce ultrasonic waves that pass through the solution and aerosolize it at the surface of the solution. The ultrasonic nebulizer creates particle sizes of about 1–6 μm MMAD, depending on the manufacturer of the device.[140] The volume output of the ultrasonic nebulizer is about 1–6 mL/min, depending on the manufacturer of the device.[140]

An ultrasonic nebulizer has 3 components: the power unit, the transducer, and a fan. The power unit converts electrical energy to high-frequency ultrasonic waves at a frequency of 1.3–2.3 megahertz.[140] The frequency of the ultrasonic waves determines the size of the particles, with an inverse relationship between frequency and particle size. The frequency is not user adjustable. The power unit also controls the amplitude of the ultrasonic waves. This is user adjustable, with an increase in amplitude resulting in an increase in output from the ultrasonic nebulizer. The transducer vibrates at the frequency of the ultrasonic waves applied to it (piezoelectric effect). The transducer is found in two shapes, concave (focused) and flat (unfocused).[140] Concave transducers produce a higher output but require a constant level of solution for proper operation. The conversion of ultrasonic energy to mechanical energy by the transducer produces heat, which is absorbed by the solution over the transducer.

Table 5. Factors Affecting Output from Ultrasonic Nebulizers

Fluid characteristics: density, viscosity, surface tension, vapor pressure
Piezoelectric transducer: frequency of vibration, amplitude of vibration, configuration (focused or flat)
Coupling of medication chamber to transducer
Medication chamber: size, baffles
Flow from fan

In some ultrasonic nebulizers, the solution to be nebulized is placed directly over the transducer. In others, the solution to be nebulized is placed into a nebulization chamber and a water couplant chamber is placed between the transducer and the medication chamber. A fan is used to deliver the aerosol produced by the ultrasonic nebulizer to the patient, or the aerosol is evacuated from the nebulization chamber by the inspiratory flow of the patient.

Summary

Nebulizers have been used clinically for many years. Despite the increasing use of metered-dose inhalers and dry powder inhalers, it is likely that nebulizers will continue to be used in selected patients. A number of factors affect nebulizer performance, and these should be appreciated by clinicians who use these devices. Several new designs have recently become available that improve the performance of the nebulizer, but their cost-effectiveness remains to be determined.

REFERENCES

1. AARC Clinical Practice Guideline. Selection of aerosol delivery device. American Association for Respiratory Care. Respir Care 1992;37(8):891–897.
2. O'Donohue WJ Jr. Guidelines for the use of nebulizers in the home and at domiciliary sites: report of a consensus conference. NAM-DRC Consensus Group. Chest 1996;109(3):814–820.
3. Turner MO, Gafni A, Swan D, FitzGerald JM. A review and economic evaluation of bronchodilator delivery methods in hospitalized patients. Arch Intern Med 1996;156(18):2113–2118.
4. Cates CJ. Holding chambers versus nebulizers for beta-agonist treatment of acute asthma. The Cochrane Database or Systematic Reviews, 1999.
5. Dalby RN, Tiano SL, Hickey AJ. Medical devices for the delivery of therapeutic aerosols to the lungs. In: Hickey AJ, editor. Inhalation aerosols: physical and biological basis for therapy. New York: Marcel Decker; 1996: 441–473.
6. Newman SP. Aerosol generators and delivery systems. Respir Care 1991;36(9):939–951.
7. Dennis JH, Hendrick DJ. Design characteristics for drug nebulizers. J Med Eng Technol 1992;16(2):63–68.
8. Smye SW, Jollie MI, Littlewood JM. A mathematical model of some aspects of jet nebuliser performance. Clin Phys Physiol Meas 1991;12(3):289–300.
9. Niven RW, Brain JD. Some functional characteristics of air-jet nebulizers. Int J Pharm 1994;104:73–85.
10. Nerbrink O, Dahlback M, Hansson HC. Why do medical nebulizers difffer in their output and particle size characteristics? J Aerosol Med 1994;7:259–276.

11. Fuller HD, Dolovich MB, Chambers C, Newhouse MT. Aerosol delivery during mechanical ventilation: a predictive in vitro lung model. J Aerosol Med 1992;5:251–259.
12. AARC Clinical Practice Guideline. Selection of device, administration of bronchodilator, and evaluation of response to therapy in mechanically ventilated patients. American Association for Respiratory Care. Respir Care 1999;44(1):105–113.
13. Diot P, Morra L, Smaldone GC. Albuterol delivery in a model of mechanical ventilation: comparison of metered-dose inhaler and nebulizer efficiency. Am J Respir Crit Care Med 1995;152(4 Pt 1):1391–1394.
14. O'Riordan TG, Greco MJ, Perry RJ, Smaldone GC. Nebulizer function during mechanical ventilation. Am Rev Respir Dis 1992;145(5): 1117–1122.
15. Niven RW. Atomization and nebulizers. In: Hickey AJ, editor. Inhalation aerosols: physical and biological basis for therapy. New York: Marcel Decker; 1996: 273–312.
16. Everard ML, Evans M, Milner AD. Is tapping jet nebulisers worthwhile? Arch Dis Child 1994;70(6):538–539.
17. Malone RA, Hollie MC, Glynn-Barnhart A, Nelson HS. Optimal duration of nebulized albuterol therapy. Chest 1993;104(4):1114–1118.
18. Phipps PR, Gonda I. Droplets produced by medication nebulizers: some factors affecting their size and solute concentration. Chest 1990;97(6):1327–1332.
19. Wood JA, Wilson RSE, Bray C. Changes in salbutamol concentration in the reservoir solution of a jet nebulizer. Br J Dis Chest 1986;80(2):164–169.
20. Stapleton KW, Finlay WH. Determining solution concentration within aerosol droplets output by jet nebulizers. J Aerosol Sci 1995; 26:137–145.
21. O'Callaghan C, Clarke AR, Milner AD. Inaccurate calculation of drug output from nebulisers. Eur J Pediatr 1989;148(5):473–474.
22. Tandon R, McPeck M, Smaldone GC. Measuring nebulizer output: aerosol production vs gravimetric analysis. Chest 1997;111(5):1361–1365.
23. Clay MM, Pavia D, Newman SP, Lennard-Jones T, Clarke SW. Assessment of jet nebulisers for lung aerosol therapy. Lancet 1983; 2(8350):592–594.
24. Aerosol consensus statement—1991. American Association for Respiratory Care. Respir Care 1991;36(9):916–921.
25. Hess D, Fisher D, Williams P, Pooler S, Kacmarek RM. Medication nebulizer performance: effects of diluent volume, nebulizer flow, and nebulizer brand. Chest 1996;110(2):498–505.
26. Loffert DT, Ikle D, Nelson HS. A comparison of commercial jet nebulizers. Chest 1994;106(6):1788–1792.
27. Alvine GF, Rodgers P, Fitzsimmons KM, Ahrens RC. Disposable jet nebulizers. How reliable are they? Chest 1992;101(2):316–319.
28. Hollie MC, Malone RA, Skufca RM, Nelson HS. Extreme variability in aerosol output of the DeVilbiss 646 jet nebulizer. Chest 1991;100(5):1339–1344.
29. Langford SA, Allen MB. Salbutamol output from two jet nebulizers. Respir Med 1993;87(2):99–103.
30. Ho SL, Coates AL. Effect of dead volume on the efficiency and the cost to deliver medications in cystic fibrosis with four disposable nebulizers. Can Respir J 1999;6(3):253–260.
31. Coates AL, MacNeish CF, Lands LC, Meisner D, Kelemen S, Vadas EB. A comparison of the availability of tobramycin for inhalation from vented vs unvented nebulizers. Chest 1998;113(4): 951–956.
32. Arossa W, Quagliotti F, Sala M, Spinaci S. De Candussio G. Different performance of two commercial nebulizers. Respiration 1984; 46(1):128–132.
33. Hess D, Horney D, Snyder T. Medication-delivery performance of eight small-volume, hand-held nebulizers: effects of diluent volume, gas flowrate, and nebulizer model. Respir Care 1989;34(8): 717–723.
34. Hurley PK, Smye SW, Cunliffe H. Assessment of antibiotic aerosol generation using commercial jet nebulizers. J Aerosol Med 1994; 7(3):217–228.
35. Smaldone GC, Perry RJ, Deutsch DG. Characteristics of nebulizers used in the treatment of AIDS-related pneumocystis carinii pneumonia. J Aerosol Med 1988;1:113–126.
36. Waldrep JC, Keyhani K, Black M, Knight V. Operating characteristics of 18 different continuous-flow jet nebulizers with beclomethasone dipropionate liposome aerosol. Chest 1994;105(1):106–110.
37. Hartley-Sharpe CJ, Booth H, Johns DP, Walters EH. Differences in aerosol output and airways responsiveness between the DeVilbiss 40 and 45 hand held nebulisers. Thorax 1995;50(6):635–638.
38. MacNeish CF, Meisner D, Thibert R, Kelemen S, Vadas EB, Coates AL. A comparison of pulmonary availability between Ventolin (albuterol) nebules and Ventolin (albuterol) Respirator Solution. Chest 1997;111(1):204–208.
39. Coates AL, MacNeish CF, Meisner D, Kelemen S, Thibert R, MacDonald J, Vadas E. The choice of jet nebulizer, nebulizing flow, and addition of albuterol affects the output of tobramycin aerosols. Chest 1997;111(5):1206–1212.
40. Newman SP, Woodman G, Clarke SW. Deposition of carbenicillin aerosols in cystic fibrosis: effects of nebuliser system and breathing pattern. Thorax 1988;43(4):318–322.
41. O'Doherty M, Thomas S, Page C, Bradbeer C, Nunan T, Bateman N. Pulmonary deposition of nebulised pentamidine isethionate: effect of nebuliser type, dose, and volume of fill. Thorax 1990;45(6): 460–464.
42. Hardy JG, Newman SP, Knoch M. Lung deposition from four nebulizers. Respir Med 1993;87(6):461–465.
43. Johnson MA, Newman SP, Bloom R, Talaee N, Clarke SW. Delivery of albuterol and ipratropium bromide from two nebulizer systems in chronic stable asthma: efficacy and pulmonary deposition. Chest 1989;96(1):6–10.
44. Standaert TA, Morlin GL, Williams-Warren J, Joy P, Pepe MS, Weber A, Ramsey BW. Effects of repetitive use and cleaning techniques of disposable jet nebulizers on aerosol generation. Chest 1998;114(2):577–586.
45. Kradjan WA, Lakshminarayan S. Efficiency of air compressor-driven nebulizers. Chest 1985;87(4):512–516.
46. Hadfield JW, Windebank WJ, Bateman JRM. Is driving gas flow rate clinically important for nebulizer therapy? Br J Dis Chest 1986; 80(1):50–54.
47. Clay MM, Pavia D, Newman SP, Clarke SW. Factors influencing the size distribution of aerosols from jet nebulisers. Thorax 1983; 38(10):755–759.
48. Everard ML, Clark AR, Milner AD. Drug delivery from jet nebulisers. Arch Dis Child 1992;67(5):586–591.
49. Flament MP, Leterme P, Burnouf T, Gayot A. Influence of formulation on jet nebulisation quality of alpha 1 protease inhibitor. Int J Pharm 1999;178(1):101–109.
50. Hess DR, Acosta FL, Ritz RH, Kacmarek RM, Camargo CA Jr. The effect of heliox on nebulizer function using a beta-agonist bronchodilator. Chest 1999;115(1):184–189.
51. Martonen T, Yang Y. Deposition mechanics of pharmaceutical particles in human airways. In: Hickey AJ, editor. Inhalation aerosols: physical and biological basis for therapy New York: Marcel Decker; 1996: 3–27.
52. Smaldone GC. Drug delivery via aerosol systems: concept of "aerosol inhaled". J Aerosol Med 1991;4(3):229–235.

53. Steventon RD, Wilson RSE. Facemask or mouthpiece for delivery of nebulized bronchodilator aerosols? Br J Dis Chest 1981;75(1): 88–90.
54. Everard ML, Hardy JG, Milner AD. Comparison of nebulised aerosol deposition in the lungs of healthy adults following oral and nasal inhalation. Thorax 1993;48(10):1045–1046.
55. Lowenthal D, Kattan M. Facemasks versus mouthpieces for aerosol treatment of asthmatic children. Pediatr Pulmonol 1992;14(3):192–196.
56. Smedsaas-Lofvenberg A, Nilsson K, Moa G, Axelsson I. Nebulization of drugs in a nasal CPAP system. Acta Paediatr 1999;88(1): 89–92.
57. Parkes SN, Bersten AD. Aerosol kinetics and bronchodilator efficacy during continuous positive airway pressure delivered by face mask. Thorax 1997;52(2):171–175.
58. Kairaitis K, Garlick SR, Wheatley JR, Amis TC. Route of breathing in patients with asthma. Chest 1999;116(6):1646–1652.
59. Melchor R, Biddiscombe MF, Mak VHF, Short MD, Spiro SG. Lung deposition patterns of directly labelled salbutamol in normal subjects and in patients with reversible airflow obstruction. Thorax 1993;48(5):506–511.
60. Pavia D, Thompson ML, Clarke SW, Shannon HS. Effect of lung function and mode of inhalation on penetration of aerosol into the human lung. Thorax 1977;32(2):194–197.
61. Lipworth BJ, Clarke DJ. Effects of airway calibre on lung delivery of nebulised salbutamol. Thorax 1997;52(12):1036–1039.
62. Swift DL, Carpin JC, Mitzner W. Pulmonary penetration and deposition of aerosols in different gases: fluid flow effects. Ann Occup Hyg 1982;26(1–4):109–117.
63. Svartengren M, Anderson M, Philipson K, Camner P. Human lung deposition of particles suspended in air or in helium/oxygen mixture. Exp Lung Res 1989;15(4):575–585.
64. Esch JL, Specktor DM, Lippmann M. Effect of lung airway branching pattern and gas composition on particle deposition: II. Experimental studies in human and canine lungs. Exp Lung Res 1988; 14(3):321–348.
65. Anderson M, Svartengren M, Bylin G, Philipson K, Camner P. Deposition in asthmatics of particles inhaled in air or in helium-oxygen. Am Rev Respir Dis 1993;147(3):524–528.
66. Anderson M, Svartengren M, Philioson K, Camner P. Deposition in man of particles suspended in air or in helium-oxygen mixture at different flow rates. J Aerosol Med 1990;3:209–216.
67. Henderson SO, Acharya P, Kilaghbian T, Perez J, Korn CS, Chan LS. Use of heliox-driven nebulizer therapy in the treatment of acute asthma. Ann Emerg Med 1999;33(2):141–146.
68. Pollack CV Jr, Fleisch KB, Dowsey K. Treatment of acute bronchospasm with beta-adrenergic agonist aerosols delivered by a nasal bilevel positive airway pressure circuit. Ann Emerg Med 1995; 2(65):552–557.
69. Dhand R, Tobin MJ. Bronchodilator delivery with metered-dose inhalers in mechancically ventilated patients. Eur Respir J 1996;9: 585–595.
70. Dhand R, Tobin MJ. Inhaled bronchodilator therapy in mechanically-ventilated patients (review). Am J Respir Crit Care Med 1997; 156(1):3–10.
71. Mantous CA, Hall JB. Administration of therapeutic aerosols to mechanically ventilated patients (review). Chest 1994;106(2):560–571.
72. Hess D. Inhaled bronchodilators during mechanical ventilation: delivery techniques, evaluation of response, and cost-effectiveness. Respir Care 1994;39(2):105–122.
73. Fink JB, Tobin MJ, Dhand R. Bronchodilator therapy in mechanically ventilated patients. Respir Care 1999;44(1):53–69.
74. Craven DE, Lichtenberg DA, Goularte TA, Make BJ, McCabe WR. Contaminated medication nebulizers in mechanical ventilator circuits: source of bacterial aerosols. Am J Med 1984;77(5):834–838.
75. Beaty CD, Ritz RH, Benson MS. Continuous in-line nebulizers complicate pressure support ventilation. Chest 1989;96(6):1360–1363.
76. Hanhan U, Kissoon N, Payne M, Taylor C, Murphy S, DeNicola LK. Effects of in-line nebulization on preset ventilatory variables. Respir Care 1993;38(5):474–478.
77. Marik P, Hogan J, Krikorian J. A comparison of bronchodilator therapy delivered by nebulization and metered-dose inhaler in mechanically ventilated patients. Chest 1999;115(6):1653–1657.
78. Dennis JH. A review of issues relating to nebulizer standards. J Aerosol Med 1998;11 Suppl 1:S73–S77.
79. Pisut FM. Comparison of medication delivery by T-nebulizer with inspiratory and expiratory reservoir. Respir Care 1989;34(11):985–988.
80. Marshall LM, Francis PW, Khafagi FA. Aerosol deposition in cystic fibrosis using an aerosol conservation device and a conventional jet nebulizer. J Paediatr Child Health 1994;30(1):65–67.
81. Thomas SH, Langford JA, George RDG, Geddes DM. Improving the efficacy of drug administration with jet nebulizers (letter). Lancet 1988;1(8577):126.
82. Piper SD. In vitro comparison of the Circulaire and AeroTee to a traditional nebulizer T-Piece with corrugated tubing. Respir Care 2000;45(3):313–319.
83. Mason JW, Miller WC, Small S. Comparison of aerosol delivery via Circulaire system vs conventional small volume nebulizer. Respir Care 1994;39(12):1157–1161.
84. Mason JW, Miller WC. Comparison of aerosol delivery via circulaire nebulizer system versus a disposable nebulizer in COPD patients. Respir Care 1996;41(11):1006–1008.
85. Hoffman L, Smithline H. Comparison of Circulaire to conventional small volume nebulizer for the treatment of bronchospasm in the emergency department. Respir Care 1997;42(12):1170–1174.
86. Newnham DM, Lipworth BJ. Nebuliser performance, pharmacokinetics, airways and systemic effects of salbutamol given via a novel nebuliser system ("Venstream"). Thorax 1994;49(8):762–770.
87. Newman SP, Pitcairn GR, Hooper G, Knoch M. Efficient drug delivery to the lungs from a continuously operated open-vent nebulizer and low pressure compressor system. Eur Respir J 1994;7(6): 1177–1181.
88. Devadason SG, Everard ML, Linto JM. Le Souef PN. Comparison of drug delivery from conventional versus "Venturi" nebulizers. Eur Respir J 1997;10(11):2479–2483.
89. Barry PW, O'Callaghan C. The output of budesonide from nebulizers. J Allergy Clin Immunol 1998;102(2):321–322.
90. Snez DS, Chai H. A standard method of intermittent inhaled therapy via a jet nebulizer. Ann Allergy 1986;57(4):245–248.
91. McPeck M, O'Riordan TG, Smaldone GC. Choice of mechanical ventilator: influence on nebulizer performance. Respir Care 1993; 38(8):887–895.
92. Hughes JM, Saez J. Effects of nebulizer mode and position in a mechanical ventilator circuit on dose efficiency. Respir Care 1987; 32(12):1131–1135.
93. Portnoy J, Aggarwal J. Continuous terbutaline nebulization for the treatment of severe exacerbations of asthma in children. Ann Allergy 1988;60(4):368–371.
94. Moler FW, Hurwitz ME, Custer JR. Improvement in clinical asthma score and PaCO2 in children with severe asthma treated with continuously nebulized terbutaline. J Allergy Clin Immunol 1988;81(6): 1101–1109.

95. Calcacone A, Wolkove N, Stern E, Afilalo M, Rosental TM, Kreisman H. Continuous nebulization of albuterol (salbutamol) in acute asthma. Chest 1990;97(3):693–697.
96. Papo MC, Frank J, Thompson AE. A prospective, randomized study of continuous versus intermittent nebulized albuterol for severe status asthmaticus in children. Crit Care Med 1993;21(10):1479–1486.
97. Lin RY, Sauter D, Newman T, Sirleaf J, Walters J, Tavakol M. Continuous versus intermittent albuterol nebulization in the treatment of acute asthma. Ann Emerg Med 1993;22(12):1847–1853.
98. Rudnitsky GS, Eberlein RS, Schoffstall JM, Mazur JE, Spivey WH. Comparison of intermittent and continuosly nebulized albuterol for treatment of asthma in an urban emergency department. Ann Emerg Med 1993;22(12):1842–1846.
99. Lin RY, Smith AJ, Hergenroeder P. High serum albuterol levels and tachycardia in adult asthmatics treated with high-dose continuously aerosolized albuterol. Chest 1993;103(1):221–225.
100. Katz RW, Kelly HW, Crowley MR, Grad R, McWilliams BC, Murphy SJ. Safety of continuously nebulized albuterol for bronchospasm in infants and children. Pediatrics 1993;92(5):666–669.
101. Olshaker J, Jerrard D, Barish RA, Brandt G, Hooper F. The efficacy and safety of a continuous albuterol protocol for the treatment of acute adult asthma attacks. Am J Emerg Med 1993;11(2):131–133.
102. Reisner C, Kotch A, Dworkin G. Continuous versus frequent intermittent nebulization of albuterol in acute asthma: a randomized, prospective study. Ann Allergy Asthma Immunol 1995;75(1):41–47.
103. Moler FW, Johnson CE, Van Laanen C, Palmisano JM, Nasr SZ, Akingbola O. Continuous versus intermittent nebulized terbutaline: plasma levels and effects. Am J Respir Crit Care Med 1995;151(3 Pt 1):602–606.
104. Shrestha M, Bidadi K, Gourlay S, Hayes J. Continuous vs intermittent albuterol, at high and low doses, in the treatment of severe acute asthma in adults. Chest 1996;110(1):42–47.
105. Baker EK, Willsie SK, Marinac JS, Salzman GA. Continuously nebulized albuterol in severe exacerbations of asthma in adults: a case controlled study. J Asthma 1997;34:521–530.
106. Weber EJ, Levitt MA, Covington JK, Gambrioli E. Effect of continuously nebulized ipratropium bromide plus albuterol on emergency department length of stay and hospital admission rates in patients with acute bronchospasm: a randomized, controlled trial. Chest 1999;115(4):937–944.
107. Portnoy J, Nadel G, Amado M, Willsie-Ediger S. Continuous nebulization for status asthmaticus (review). Ann Allergy 1992;69(1):71–79.
108. Voss KR, Willsie-Ediger SK, Pyszczynske DR, Nelson KA. Description of a delivery method for continuously aerosolized albuterol in status asthmaticus. J Asthma 1990;27(1):37–39.
109. Chipps BE, Blackney DA, Black LE, Moody RR, Marino JT, Ridell RC, Wong GA. Vortran high output extended aerosol respiratory therapy (HEART) for delivery of continuously nebulized terbutaline for the treatment of acute bronchospasm. Pediatr Asthma Allergy Immunol 1990;471–277.
110. Berlinski A, Waldrep JC. Four hours of continuous albuterol nebulization. Chest 1998;114(3):847–853.
111. Reisner C, Lee J, Kotch A, Dworkin G. Comparison of volume output from two different continuous nebulizer systems. Ann Allergy Asthma Immunol 1996;76(2):209–213.
112. Raabe OG, Wong TM, Wong GB, Roxburgh JW, Piper SD, Lee JI. Continuous nebulization therapy for asthma with aerosols of beta2 agonists. Ann Allergy Asthma Immunol 1998;80(6):499–508.
113. McPeck M, Tandon R, Hughes K, Smaldone GC. Aerosol delivery during continuous nebulization. Chest 1997;111(5):1200–1205.
114. Corkery KJ, Luce JM, Montgomery AB. Aerosolized pentamidine for treatment and prophylaxis of *Pneumocystis carinii* pneumonia: an update. Respir Care 1988;33(8):676–685.
115. Vinciguerra C, Smaldone G. Treatment time and patient tolerance for pentamidine delivery by Respirgard II and AeroTech II. Respir Care 1990;35(11):1037–1041.
116. Matthys H, Herceg R. Dosing strategies for aerosol delivery to the lung parenchyma, with specific recommendations for pentamidine. Respir Care 1991;36(9):989–993.
117. Demers RR, Parker J, Frankel LR, Smith DW. Administration of ribavirin to neonatal and pediatric patients during mechanical ventilation. Respir Care 1986;31(12):1188–1195.
118. American Academy of Pediatrics Committee on Infectious Diseases. Use of ribavirin in the treatment of respiratory syncytial virus infection. Pediatrics 1993;92(3):501–504.
119. Smith DW, Frankel LR, Mathers LH, Tang AT, Ariagno RL, Prober CG. A controlled trial of aerosolized ribavirin in infants receiving mechanical ventilation for severe respiratory syncytial virus infection. N Engl J Med 1991;325(1):24–29.
120. Kacmarek RM, Kratohvil J. Evaluation of a double-enclosure double-vacuum unit scavenging system for ribavirin administration. Respir Care 1992;37(1):37–45.
121. Charney W, Corkery KJ, Kraemer R, Wugofski L. Engineering and administrative controls to contain aerosolized ribavirin: results of simulation and application to one patient. Respir Care 1990;35(11):1042–1048.
122. Wahlin B, Malmstrom B, Soop M, Hellstrom LG. A pediatric canopy system for aerosol administration and minimized environmental pollution. Acta Anaesthesiol Scand 1996;40(8 Pt 1):932–939.
123. Stevens HR, Albregt HB. Assessment of ultrasonic nebulization. Anesthesiology 1966;27(5):648–653.
124. Modell JH, Giammona ST, Davis JH. Effect of chronic exposure to ultrasonic aerosols on the lung. Anesthesiology 1967;28(4):680–688.
125. Dennis JH, Stenton SC, Beach JR, Avery AJ, Walters EH, Hendrick DJ. Jet and ultrasonic nebuliser output: use of a new method for direct measurement of aerosol output. Thorax 1990;45(10):728–732.
126. Newman SP, Pellow GD, Clarke SW. In vitro comparison of DeVilbiss jet and ultrasonic nebulizers. Chest 1987;92(6):991–994.
127. Fok TF, Lam K, Ng PC, So HK, Cheung KL, Wong W, So KW. Randomised crossover trial of salbutamol aerosol delivered by metered-dose inhaler, jet nebuliser, and ultrasonic nebuliser in chronic lung disease. Arch Dis Child Fetal Neonatal Ed 1998;79(2):F100–F104.
128. Ballard RD, Bogin RM, Pak J. Assessment of bronchodilator response to a beta-adrenergic delivered from an ultrasonic nebulizer. Chest 1991;100(2):410–415.
129. Nakanishi AK, Lamb BM, Foster C, Rubin BK. Ultrasonic nebulization of albuterol is no more effective than jet nebulization for the treatment of acute asthma in children. Chest 1997;111(6):1505–1508.
130. Larsen KR, Svendsen UG, Molgaard F, Petersen BN. Comparability of albuterol delivered by a piezoelectric device versus metered-dose inhaler in patients with chronic obstructive airways disease. J Aerosol Med 1998;11(2):81–88.
131. Olivenstein R, Wolkove N, Cohen C, Frank H, Kreisman H. A comparison of responses to albuterol delivered by two aerosol devices. Chest 1986;90(3):392–395.
132. Eisenberg J, Pepe M, Williams-Warren J, Vasiliev M, Montgomery AB, Smith AL, Ramsey BW. A comparison of peak sputum tobramycin concentration in patients with cystic fibrosis using jet and ultrasonic nebulizer systems. Aerosolized Tobramycin Study Group. Chest 1997;111(4):955–962.

133. O'Riordan TG, Amram JC. Effect of nebulizer configuration on delivery of aerosolized tobramycin. J Aerosol Med 1997;10(1):13–23.
134. Weber A, Morlin G, Cohen M, Williams-Warren J, Ramsey B, Smith A. Effect of nebulizer type and antibiotic concentration on device performance. Pediatr Pulmonol 1997;23(4):249–260.
135. Weber A, Smith A, Williams-Warren J, Ramsey B, Covert DS. Nebulizer delivery of tobramycin to the lower respiratory tract. Pediatr Pulmonol 1994;17(5):331–339.
136. Harvey CJ, O'Doherty MJ, Page CJ, Thomas SHL, Nunan TO, Treacher DF. Comparison of jet and ultrasonic nebulizer pulmonary aerosol deposition during mechanical ventilation. Eur Respir J 1997; 10(4):905–909.
137. Thomas SH, O'Doherty MJ, Page CJ, Treacher DF, Nunan TO. Delivery of ultrasonic nebulized aerosols to a lung model during mechanical ventilation. Am Rev Respir Dis 1993;148(4 Pt 1):872–877.
138. Kemming GI, Kreyling W, Habler O, Merkel M, Kleen M, Welte M, et al. Aerosol production and aerosol droplet size distribution during mechanical ventilation (IPPV) with a new ultrasonic nebulizer. Eur J Med Res 1996;1(7):321–327.
139. Williams L, Fletcher GC, Daniel M, Kinsella J. A simple in vitro method for the evaluatin of an ultrasonic nebulizer for drug delivery to intubated, ventilated patients and the effect of nebulizer and ventilator settings on the uptake of fluid from the nebulizer chamber. Eur J Anaesthesiol 1999;16(7):479–484.
140. Greenspan BJ. Ultrasonic and electrohydrodynamic methods for aerosol generation. In: Hickey AJ, editor. Inhalation aerosols: physical and biological basis for therapy. New York: Marcel Decker; 1996: 313–335.
141. Gale AE. Drug degeneration during ultrasonic nebulization. J Aerosol Sci 1985;16:265.

Metered-Dose Inhalers, Dry Powder Inhalers, and Transitions

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Montreal Protocol
Summary

[Respir Care 2000;45(6):623–635] *Key words: pressurized metered-dose inhaler, spacer, valved holding chamber, dry powder inhaler, chlorofluorocarbon, hydrofluoroalkane, aerosol.*

Introduction

Pressurized metered-dose inhalers (pMDIs) are the most common devices, around the world, for therapeutic aerosol delivery, with more than 440 million pMDIs produced in 1998 and production of pMDIs estimated to reach 800 million by the year 2000.[1] Next to the tablet (pill), the pMDI is the most common form of medication. As recently as 45 years ago, the only available option for a portable hand-held system of aerosol therapy was the hand bulb nebulizer. The hand bulb nebulizer was relatively fragile and did not provide consistent aerosol output or multidose convenience.

In 1955, the 13-year-old asthmatic daughter of Dr George Maison, President of Riker Laboratories (a wholly-owned subsidiary of Rexall Drug Company, now 3M Pharmaceuticals) asked her father "why can't they put my asthma medicine in a spray-can like they do hair spray?" Dr Maison asked Mr Irving Porush, the head chemist in Riker's three-person pharmaceutical development lab, to develop a pressurized inhaler for delivery of a bronchodilator. Armed with some propellant from Du Pont (FREON 12 and 114), an old ice cream freezer from the Rexall drug store downstairs, a case of empty soda bottles, and a bottle capper, the first pMDI was born. Within a matter of months, the first pMDIs with salts of isoproterenol and epinephrine were developed, using a 50 μL metering valve developed for perfume aerosols, a 10 mL amber vial, and a 3-inch-long plastic mouthpiece with a molded nozzle.[2] In June of 1955, the first clinical trials at the Long Beach Veterans Administration Hospital showed these first pMDIs to be effective, and new drug approvals filed in January of 1956 (documents 13 mm thick) were approved by March of the same year.[2] In 1957, a suspension of micronized drug in propellant with a surfactant was substituted for the original bronchodilators. It is interesting that, although the suspensions proved to be more effective in all pulmonary measurements, many of the previous pMDI users complained that they were not getting as much medication. Apparently, patients missed the taste of the

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alcohol present in early solution formulations, which they associated with active medication. This era represented much of the technologic innovation we are familiar with in the current chlorofluorocarbon (CFC)-propelled pMDIs. Soon thereafter, the Kefauver amendments to the food and drug laws required more complex new drug approval submissions and clinical trials.[2] This radically curtailed innovative development of pMDI technology for the next 40 years.

In 1974, the Rowland and Molena theory that CFCs were contributing to ozone depletion led to a ban of CFCs in common aerosol products.[3] By the end of the decade the ozone depletion theory was falling into disrepute, and interest in alternative propellants such as perfluoropropane was limited by the expense of toxicity testing and clinical testing. By the mid-1980s, the paperwork for a new drug approval submission for a pMDI of a new bronchodilator had grown from less than 2 cm thick to 17 volumes, and 3.5 years from submission to approval.[1]

In 1987, the Montreal protocol was signed, and refrigerant manufacturers, the primary producers of CFCs, said they would cease production of CFCs by 1996. An exemption was granted for pMDIs to use CFCs until such time as suitable alternatives could be found. This escalated the development of the dry powder inhaler (DPI), as the quest for suitable alternative propellants began in earnest.

The first alternative propellant compound to enter full-term industrial toxicity tests was hydrofluoroalkane (HFA)-134a (tetrafluroethane), which appeared to be a promising replacement for CFC-12.[4] A pharmaceutical consortium was formed to facilitate the testing required by regulatory agencies for HFA-134a and HFA-227 (heptafluoropropane). These propellants have physicochemical properties similar to the three CFCs used in pMDIs (Table 1).[4]

The goals herein are to characterize some of the key issues associated with the use of pMDIs and DPIs and to discuss their evolution in response to the transition to more environmentally benign propellants.

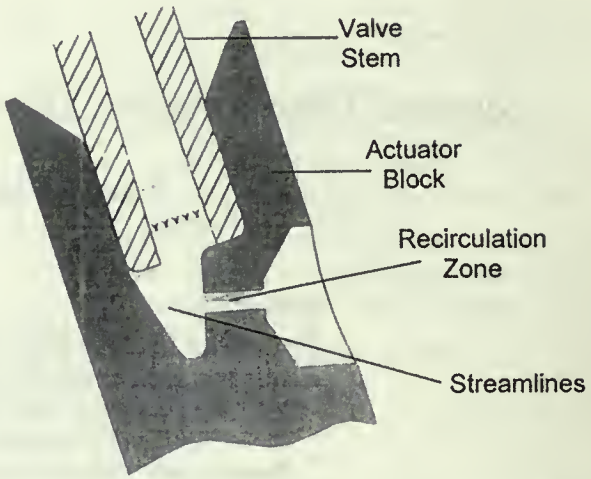

Fig. 1. Path of fluid flow in actuator nozzle of a pressurized metered-dose inhaler (pMDI). Changes in valve stem size and design of the actuator nozzle recirculation zone and actuator orifice can affect plume geometry and aerosol characteristics. The orifice diameter of the chlorofluorocarbon-propelled pMDI Ventolin (0.021 inch) is nearly twice that of the hydrofluoroalkane-propelled pMDI Proventil HFA (0.011 inch), which correlates with differences in mass median aerodynamic diameter and respirable mass. (From Reference 8, with permission.)

Pressurized Metered-Dose Inhalers

The pMDI is the most commonly prescribed method of aerosol delivery.[5] pMDIs are used to administer bronchodilators, anticholinergics, anti-inflammatory agents, and steroids. More formulations of these drugs are currently available for use via pMDI than via other nebulization systems. Properly used, pMDIs are at least as effective as other systems of aerosol generation for drug delivery.[6]

A pMDI is a pressurized canister containing a mixture of propellants, surfactants, preservatives, and flavoring agents, with approximately 1% of the total contents being active drug. This mixture is released from the canister through a metering valve and stem that fits into an actuator

Table 1. Physicochemical and Atmospheric Properties of Propellants Used in Pressured Metered-Dose Inhalers

Propellant	Formula	Common Name	Density (g/mL) at 20° C	Vapor Pressure at 20° C	Boiling Point	Atmospheric Life Years	Global Warming Potential	Ozone-Depleting Potential
HFA-134a	$C_2H_2F_4$	Tetrafluoroethane	1.21	70	−27° C	16	0.26	0
HFA-227	C_3HF_7	Heptafluoropropane	1.41	40	−17° C	33	0.3	0
CFC-11	CCl_3F	Trichlorofluoromethane	1.49	−1.8	24° C	60	1	1.0
CFC-12	CCl_2F_2	Dichlorodifluoromethane	1.33	67.6	−30° C	125	3	0.9
CFC-114	$C_2Cl_2F_4$	Dichlorotetrafluorethane	1.47	11.9	4° C	200	3.9	0.7

*Ozone-depleting potential is set relative to CFC-11, which is assigned a value of 1.0.
CFC = chlorofluorocarboo, HFA = hydrofluoroalkane.
(Adapted from Reference 4, with permission).

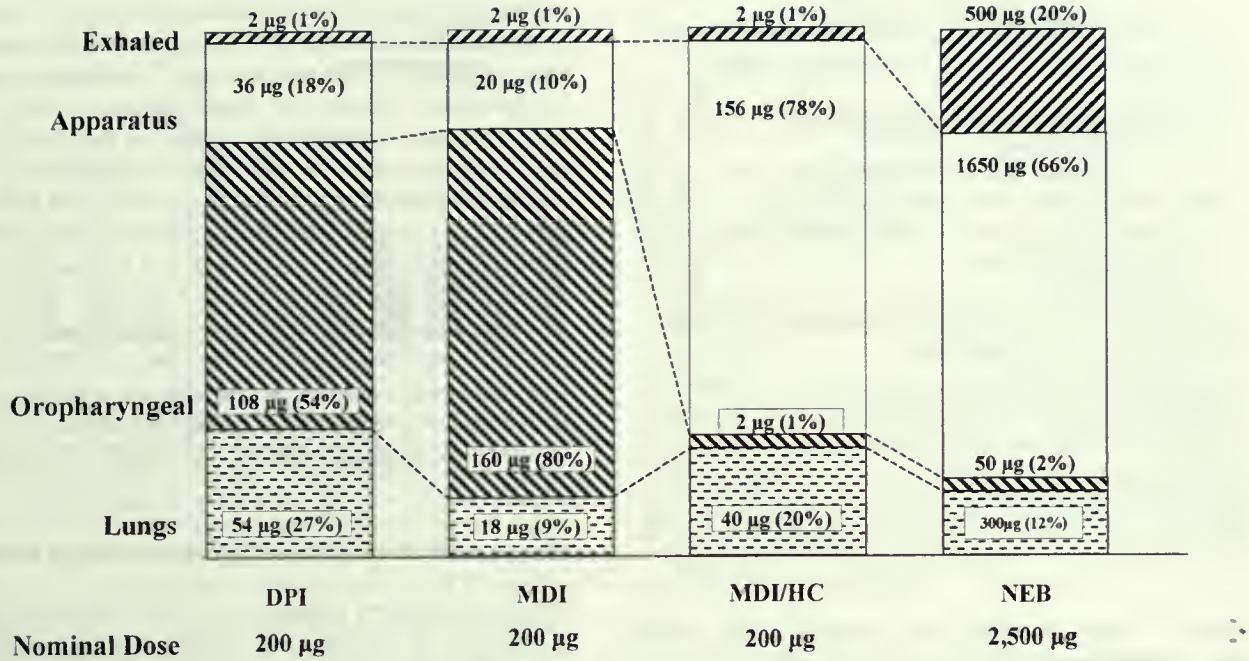

Fig. 2. Comparison of the quantity and percent of nominal dose of albuterol deposited in the lungs, oropharynx, apparatus, and exhaled, with typical use of a dry powdered inhaler (DPI), a pressurized metered-dose inhaler (pMDI), a pMDI with holding chamber (MDI/HC), and a nebulizer (NEB). Both DPI and pMDI deposit > 50% of nominal dose in the oropharynx, while pMDI/HC and NEB leave 78–80% of the dose in the apparatus. The percent of nominal dose exhaled is 20-fold greater with the nebulizer than with other devices. (Adapted from data in Reference 18 and from Fink JB, Tobin MJ, Dhand R. Bronchodilator therapy in mechanically ventilated patients. Respir Care 1999;44[1]: 53–69.)

boot designed and tested by the manufacturer to work with that specific formulation.[7] Small changes in actuator design can change a pMDI's aerosol characteristics and output (Fig. 1).[8] Dispersing agents are present in concentrations equal to or greater than that of the medication, and in some patients these dispersing agents cause coughing and wheezing.[9] The bulk of the spray (up to 80% by weight) is propellant, commonly a CFC such as FREON.[10,11] Adverse reactions to CFCs are extremely rare.[12,13]

The output volume of a pMDI ranges from 30–100 µL and contains between 20 µg and 5 mg of drug. Lung deposition is estimated at 10–25% in adults, with high intersubject variability, largely dependent on user technique. When proper technique and an accessory device is used, the pMDI delivers substantially more of the nominal dose of medication to the lung than a standard small-volume nebulizer (SVN).

Aerosol production from a pMDI takes approximately 20 milliseconds.[14] Aerosolization of the liquid released from the canister begins as the propellants vaporize or "flash," leaving the actuator in a "plume," and continues as the propellant evaporates.[15] The velocity of the liquid spray leaving the pMDI is about 15 m/s, which falls to less than half the maximum velocity within 0.1 second as the plume develops and moves away from the actuator orifice.[16] The particles produced from the "flashing" of propellants are initially 35 µm, and rapidly decrease in size because of evaporation as the plume moves away from the nozzle.[17] These aged smaller particles have been associated with a distance of ≥ 12 cm from the nozzle.[17] Because of the velocity and dispersion of the jet fired from the pMDI, approximately 80% of the dose leaving the actuator impacts and deposits in the oropharynx, especially when the canister is fired inside the mouth.[11,17] The mass median aerodynamic diameter (MMAD) of aged aerosol particles from a pMDI is 2–6 µm, with lung deposition of about 10–20%.[18] The 80% of dose deposited in the mouth may be a factor in systemic absorption, as opposed to direct aerosol delivery to the lung (Fig. 2), since the pMDI delivers a substantial amount of drug to the mucous membranes of the mouth and stomach. Unfortunately, the actual amount of drug delivered to an individual patient is unpredictable because of substantial interpatient variability.[18]

The nominal dose of medication with the pMDI is much smaller than with the nebulizer (see Fig. 2). The quantity of albuterol from a pMDI exiting the actuator nozzle is 100 µg with each actuation or 90 µg from the opening of the actuator boot (which is how pMDI aerosol output is characterized in the United States). Thus, a dose of 2 to 4 actuations (200–400 µg nominal dose) with 10% deposition of the nominal dose to the lower respiratory tract

Table 2. Optimal Technique for Using a pMDI

Warm the pMDI canister to hand or body temperature, shake vigorously.
Assemble apparatus, uncap mouthpiece and make sure there are no loose objects in the device.
Open mouth wide, keep tongue from obstructing the mouthpiece.
Hold the pMDI vertically, with the outlet aimed at mouth.
Place canister outlet between lips, or position the pMDI about 4 cm (two fingers) away from mouth.
Breathe out normally.
As you begin to breathe in slowly (<0.5 L/s), actuate (fire) the pMDI.
Continue to inhale to total lung capacity.
Hold breath for 4–10 seconds.
Wait 30 seconds between inhalations (actuations).
Disassemble apparatus, recap mouthpiece.

pMDI = pressurized metered-dose inhaler.
(Adapted from data in Reference 5.)

delivers 20–40 μg to the lung, resulting in the typical bronchodilator response.

Technique and Patient Education

Effective use of a pMDI is technique-dependent. Up to two thirds of pMDI users and health professionals who teach pMDI use do not perform the procedure properly.[19,20] Table 2 outlines recommended steps for self-administering a bronchodilator using a pMDI.[21] Good patient instruction can take 10–30 minutes and should include demonstration, practice, and confirmation of patient performance (demonstration placebo units are available from many manufacturers for this purpose). Repeated instruction improves performance.[22]

Infants, young children, the elderly, and patients in acute distress may not be able to use a pMDI effectively, even after proper instruction. This is largely associated with the need to coordinate actuation with inspiration or the inability to use the mouthpiece of the actuator. Other technology-dependent issues can also limit a patient's ability to use a pMDI. The "cold FREON" effect occurs if the cold aerosol plume (which may be 30° C below room temperature) causes the patient to stop inhaling when the plume reaches the back of the mouth.

Problems with home use of pMDI devices include poor technique of use and poor storage.[5] The pMDI should always be stored with the cap on, both to prevent foreign objects from entering the boot and to reduce humidity and microbial contamination. Pressurized pMDIs should always be discarded when empty, to avoid administering propellant without medication. Although it has been suggested that pMDIs can be tested for drug remaining by floating the canister in water, this technique can be difficult to perform and interpret, and runs the risk of contaminating the device. Infiltration of water into the canister can compromise pMDI performance. Consequently, many manufacturers actively discourage the use of the "float test." It is more accurate and reliable for the patient, parent, or care provider to note when the medication was started, the number of doses taken each day, and the number of doses in the canister, and to calculate a discard date. For example, if there are 200 actuations in a canister (and this information is always indicated on the canister label) and 4 puffs are taken per day, the canister should be discarded 50 days (7 weeks) after the start date. This discard date should be written on the canister label on the day the new canister is started. For rescue medication, patients should be encouraged to track the number of actuations used.

Pressurized Metered-Dose Inhaler Accessory Devices

A variety of pMDI accessory devices have been developed to overcome the limitations of pMDI administration (hand-breath coordination problems, cold FREON effect, and high oropharyngeal deposition). Accessory devices include flow-triggered pMDIs, spacers, and valved holding chambers.

Flow-Triggered Pressurized Metered-Dose Inhaler

The Autohaler is a flow-triggered pMDI designed to reduce the need for hand-breath coordination by firing in response to the patient's inspiratory effort.[23] To use the Autohaler, the patient cocks a lever on the top of the unit that spring-loads the canister against a vane mechanism. When the patient's inspiratory flow exceeds 30 L/min, the vane moves, allowing the canister to be pressed into the actuator, firing the pMDI. In the United States this device is only available with the β agonist pirbuterol, but other formulations are in development. The flow required to

Table 3. Optimal Technique for Using a pMDI with a Valved Holding Chamber

Warm pMDI to hand or body temperature.
Assemble apparatus and make sure there are no objects in device that could be aspirated or obstruct outflow.
Shake canister vigorously and hold canister vertically.
Place holding chamber in mouth (or place mask completely over nose and mouth), encouraging patient to breathe through mouth.
Breathe normally and actuate at the beginning of inspiration. Small children and infants should continue to breathe through the device for 5 or 6 breaths. Larger breaths with breath-holding may be encouraged in those patients who can cooperate.
Allow 30 seconds between actuations.

pMDI = pressurized metered-dose inhaler.
(Adapted from data in Reference 5.)

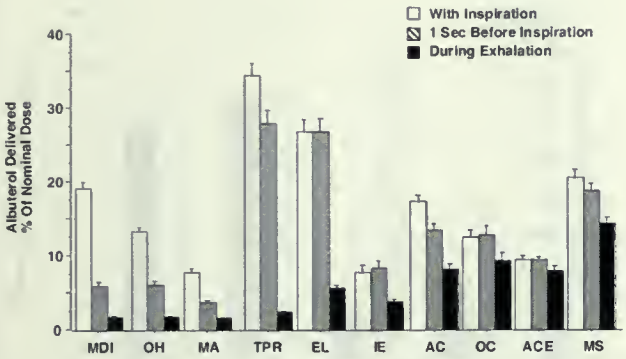

Fig. 3. The percent of albuterol delivered from a pressurized metered-dose inhaler (pMDI) actuation synchronized with inspiration, compared to actuation of an albuterol pMDI (open bars) one second before inspiration (diagonally hatched bars) and during exhalation (solid bars) for the pMDI alone, and with 9 types of accessory devices. The pMDI alone and pMDI with low-volume spacers (OH, MA) suffered similar loss of dose in both conditions. Larger spacers (TPR, EL) protected against loss of dose in the case of actuation one second before inspiration, but provided no dose protection in the case of actuation during exhalation. Bag (IE) and valved holding chambers (AC, OC, ACE, MS) both provided protection from loss of dose in both conditions. OH=OptiHaler. MA=Mist Assist. TPR=toilet paper roll. EL=Ellipse. IE=InspirEase. AC=AeroChamber. OC=OptiChamber. ACE=Aerosol Cloud Enhancer. MS=MediSpacer. (Adapted from data in Reference 24.)

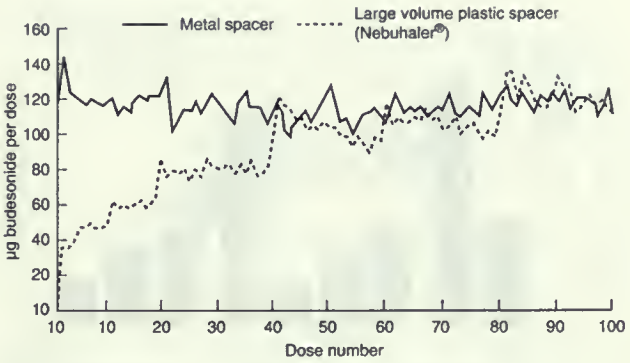

Fig. 4. The amount of budesonide delivered with each dose (actuation) of a pressurized metered-dose inhaler with a large-volume non-electrostatically-charged metal spacer (solid line) is relatively stable compared to the low initial dose available using an electrostatically charged plastic spacer (dashed line). The delivered dose with the plastic spacer increased dramatically over the first 40 doses, and then matched delivery with the metal spacer. (From Reference 32, with permission.)

actuate the device may be too great for some small children to generate, especially during acute exacerbations.

Spacers and Valved Holding Chambers

Spacers and valved holding chambers are accessory devices that, when properly designed, reduce oropharyngeal deposition of drug, ameliorate the bad taste of some medications, eliminate the cold FREON effect, and, in the case of valved holding chambers, reduce drug loss associated with poor hand-breath coordination. Table 3 outlines recommended steps for self-administering a bronchodilator using a pMDI with a valved holding chamber.

Clinicians should be careful to distinguish spacers from valved holding chambers. A spacer device is a simple open-ended tube or bag that, with sufficiently large volume, provides space for the pMDI plume to expand by allowing the CFC propellant to evaporate. To perform this function, a spacer device must have an internal volume of over 100 mL, and provide a distance of 10–13 cm between the pMDI nozzle and the first wall or baffle in the plume's path. Smaller low-volume spacers can reduce respiratory dose by 60% and offer no protection against poor coordination between actuation and breathing pattern. Spacers with internal volumes greater than 100 mL generally provide some protection against loss of dose from early firing of the pMDI, although exhaling immediately following the actuation clears most of the aerosol from the device, wasting the dose.

The valved holding chamber (usually 140–750 mL) allows the plume to expand, and incorporates a one-way valve that permits the aerosol to be drawn from the chamber during inhalation only, diverting exhaled gas to the atmosphere and not disturbing remaining aerosol suspended in the chamber. Thus, the valved holding chamber combines the benefits of a spacer with the advantage of protecting the patient from loss of dose due to poor hand-breath coordination.

Fink et al[24] performed in vitro testing of drug delivered from a pMDI alone and from a pMDI in combination with a variety of spacers and holding chambers, when actuation of the pMDI was (1) synchronized with the beginning of inspiration, (2) one second before inspiration, or (3) during exhalation. Figure 3 shows the mean proportion of drug available to the lower respiratory tract with pMDI and a variety of small-volume spacers, large-volume spacers, bag holding chambers, and valved holding chambers. The pMDI alone and small-volume spacers offered little protection against drug loss with actuation 1 second before inhalation or with actuation during exhalation. The large-volume spacers offered good dose protection with actuation 1 second before inhalation, but not with actuation during exhalation.[24] The valved holding chambers provided good protection with actuation 1 second before inhalation, and 70% of baseline dose when the pMDI was actuated during exhalation.

A patient with a small tidal volume may use multiple breaths to empty the aerosol from the chamber,[3–6] except when there is an exceptionally large dead space. A valved holding chamber can also incorporate a mask to allow effective pMDI administration in a patient who is unable

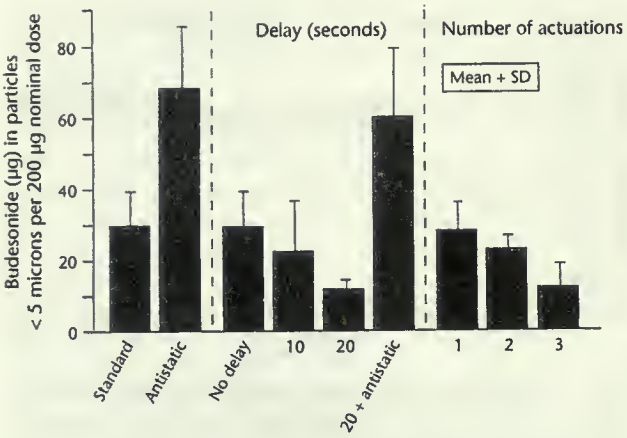

Fig. 5. Respirable dose of budesonide available with a standard spacer and with an antistatic spacer, with no delay in actuation (left), delays of 10 seconds and 20 seconds (center), and with multiple actuations from the pMDI into the standard plastic spacer (right). (From Reference 35, with permission.)

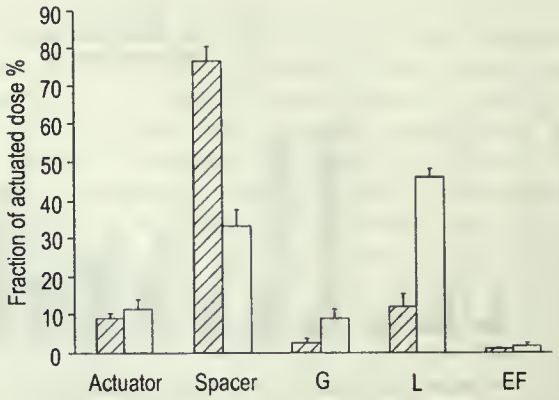

Fig. 6. Relative deposition of salbutamol, expressed as a percentage of total actuated dose, in the actuator, spacer, gastrointestinal tract (mouth, throat, esophagus, and stomach [G]), lung (L), and expiratory filter (EF) after inhalation through electrostatically charged (diagonally hatched bars) and non-electrostatically-charged, detergent-coated Volumatic spacer (clear bars) in 8 healthy adults. Values are means and standard deviations. (From Reference 36, with permission.)

to use a mouthpiece because of size, age, coordination, or mental status.[5] For use with infants, it is critical that these masks have minimal dead space, be comfortable to the child's face, and that the chamber have a valve that opens or closes with the low inspiratory flow generated by an infant.

The use of a valved holding chamber should be encouraged, especially for infants and small children, and for any child with steroid administration. A valved holding chamber reduces the need to coordinate the breath with actuation, reduces oral deposition (and, therefore, bad taste), decreases cold FREON effect, and decreases MMAD, which increases respirable particle mass, improves lower respiratory tract deposition, and significantly improves therapeutic effect.[5] These devices reduce the pharyngeal deposition of aerosol 10–15-fold, compared to administration without a holding chamber. This decreases the swallowed amount, which is an important consideration with steroid administration.[25,26]

The high percentage of oropharyngeal drug deposition with steroid pMDIs can increase the risk of oral yeast infections (thrush). Rinsing the mouth after steroid use can reduce this problem, but most pMDI steroid aerosol impaction occurs deeper in the pharynx, which is not easily rinsed. For this reason, steroid pMDIs should always be used in combination with a valved holding chamber.

Wheezy Infants

Valved holding chambers make pMDIs as or more reliable than SVNs for aerosol administration.[27] Closa et al studied 34 acutely asthmatic infants, ages 1–24 months. Each subject received 2 doses of terbutaline, 20 minutes apart, as either 2 mg/dose in 2.8 mL of 0.9% saline via nebulizer or 0.5 mg/dose (5 puffs) via pMDI with valved holding chamber.[28] They found no difference in the rate of improvement or clinical score, and concluded that both devices were equally effective. Similarly, Williams et al studied 60 children, ages ≤ 6 years, suffering acute asthma exacerbations. The subjects were randomized to receive albuterol via nebulizer or via pMDI with valved holding chamber, for 3 treatments over 1 hour.[29] All patients showed improvement over baseline, with no difference between treatment groups.

To determine whether a single brief demonstration of the proper use of a valved holding chamber in the emergency department would result in improved outcomes, Cun-

Table 4. CFC and HFA MDIs in CFC, HFA, and Generic Actuators

Canister	Boot	MMAD ± GSD	Total Mass (g/m^3)
CFC	CFC	2.51 ± 2.8	3.5
CFC	HFA	1.32 ± 3.1*	1.7*
HFA	HFA	2.16 ± 2.3	4.4
HFA	CFC	4.59 ± 4.2*	1.2*
CFC	GA	2.12 ± 1.9	2.1
HFA	GA	3.52 ± 3.1*	1.1*

Values represent mean ± standard error.
CFC = chlorofluorocarbon
HFA = hydrofluoroalkane
MDI = metered-dose inhaler
MMAD = mass median aerodynamic diameter
GSD = geometric standard deviation
GA = generic actuator
*$p < 0.001$ compared to standard MDI/boot actuator.
(Adapted from data in Fink JB, Dhand R, Grychowski J, Fahey PJ, Tohin MJ. Reconciling in vitro and in vivo measurements of aerosol delivery from a metered-dose inhaler during mechanical ventilation and defining efficiency-enhancing factors. Am J Respir Crit Care Med. 1999;159[1]:63–68.)

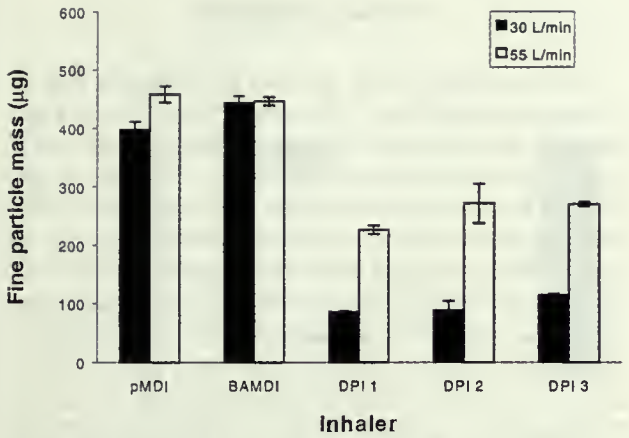

Fig. 7. The fine particle mass delivered from a 1,000 µg dose (± SD) as a function of flow. pMDI = pressurized metered-dose inhaler. BAMDI = breath-actuated pMDI (Autohaler). DPI = dry powder inhaler. DPI 1 = Rotahaler. DPI 2 = Turbuhaler. DPI 3 = Diskhaler. (From Reference 50, with permission.)

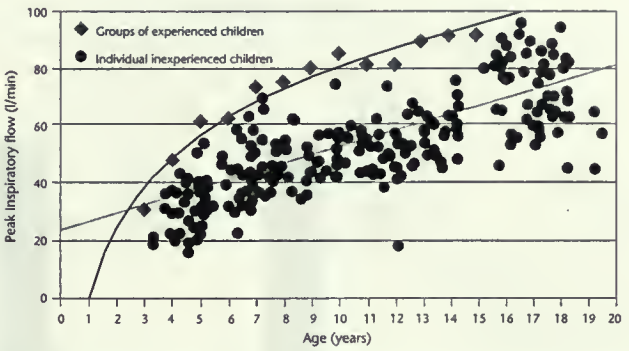

Fig. 8. Peak inspiratory flows in individual inexperienced children (filled circles) and groups of experienced children (gray diamonds). (From Reference 52, with permission.)

ningham and Crain enrolled 84 children in the emergency department to receive the inhaled medication with or without a valved holding chamber. The valved holding chamber group reported significantly faster resolution of wheezing, fewer days of cough, and fewer missed days of school ($p < 0.01$).[30]

The belief that an SVN is better than a pMDI if the patient is not able to inhale with optimal technique is not supported by research. In fact, if the patient cannot perform an optimal maneuver using a pMDI, he or she is unable to perform an optimal maneuver using an SVN. Although optimal technique is always preferred, it is often difficult to attain with an infant, small child, or severely dyspneic patient. In such cases, an alternative may be to increase the pMDI or nebulizer dose to achieve the desired outcome.

Care and Cleaning

Particles containing drug settle and deposit within the spacer or holding chamber, causing a whitish build-up on the inner chamber walls and valves. This residual drug poses no risk to the patient, but has been associated with increased variability in dose available to the patient.[31] Rau et al studied available dose from a pMDI formulation of beclomethasone for 3 spacers/holding chambers over 6 months when the devices were washed regularly, and without washing, which resulted in greater variability with all devices, but a significant increase in available dose was noted with one of the devices.[31] This effect appears to be associated with the static charge of plastic spacers. After washing a chamber or spacer with tap water, it is less effective for the next 10–40 puffs, until the static charge in the chamber (which attracts small particles) is once again reduced (Fig. 4).[32] Use of regular dish soap to wash the chamber reduces or eliminates this static charge, increasing the amount of drug available to the patient.

The effect of static charge on aerosol has been shown to have a substantial impact on the respirable dose from a pMDI available to the patient. Static charge has been shown to decrease drug availability in the case of pMDI multiple actuations.[32–35] The use of multiple actuations into a holding chamber prior to inhalation was widely recommended in the past, but studies by O'Callaghan et al[33–35] found that that technique leads to a reduction in the proportion of respirable particles within the device, with the net effect that little or no additional drug may be available to the patient, compared to a single actuation.

Because of the inherently nonconducting surface of plastic spacers, electrostatic charge inevitably accumulates on these devices and affects charge output.[33–35] Plastic spacers initially have a strong electrostatic charge that causes particle deposition inside the spacer. The static charge can be eliminated by constructing the device of metal, or on a polycarbonate spacer by coating with an antistatic paint, washing with a deionizing soap, and repeated dosing without cleaning between use. In 1995, Barry and O'Callaghan[33] found that a greater dose of budesonide from a pMDI was available from an antistatic holding chamber than from a standard holding chamber, with standard use, with delays of up to 20 seconds between actuation and inhalation, and with multiple actuations (Fig. 5).

Pierart et al compared the influence of 4 household detergents, studying the influence of dilution and the subsequent duration of antistatic effects.[36] They found that detergents reduced the surface electrostatic charge in the spacer, increasing respirable mass of albuterol by ≥ 37%, compared to a water-rinsed/drip-dried spacer, in vitro. Results lasted for 4 weeks, independent of dilution. Lung deposition of radiolabeled albuterol was 45.6% in healthy subjects with the detergent-coated spacer, compared to 11.5% through a static device. The increased lung deposition with the non-electrostatically-charged device appears

Table 5. Salbutamol CFC and HFA pMDI Formulations

	Ventolin	Airomir
Propellants	CFC-12 CFC-11	HFA-134a
Surfactant	Oleic acid	Oleic acid
Cosolvent		Ethanol
Drug	Salbutamol	Salbutamol sulfate

CFC = chlorofluorocarbon
HFA = hydrofluoroalkane
pMDI = pressurized metered-dose inhaler
(Adapted from Reference 4.)

to coincide with the reduced amount of drug remaining in the spacer (Fig. 6). The authors recommended that plastic spacers be soaked in a dilute solution of household detergent and then allowed to drip dry without water rinsing once a month.

Accessory devices either use the manufacturer-designed boot that comes with the pMDI or incorporate a "universal canister adapter" to fire the pMDI canister. Different formulations of pMDI drugs operate at different pressures and use different sizes of actuator orifice that are specifically designed exclusively for that pMDI formulation. Output characteristics of a pMDI change when using an adapter with a different size orifice (Table 4). Therefore spacers or holding chambers with universal canister adapters should be avoided and those that use the manufacturers boot with the pMDI should be used.

Dry Powder Inhalers

DPIs create aerosols by drawing air through a dose of dry powder medication.[37] The powder contains either micronized drug particles (< 5 μm MMAD) with larger lactose or glucose particles (diameter > 30μm), or micronized drug particles bound into loose aggregates.[38] Micronized particles adhere strongly to each other and to most surfaces. Addition of the larger particles of the carrier decreases cohesive forces in the micronized drug powder, so that separation into individual respirable particles (deaggregation) occurs more readily. Thus, the carrier particles aid the flow of the drug powder from the device. These carriers also act as "fillers" by adding bulk to the powder when the unit dose of a drug is very small. Usually, the drug particles are loosely bound to the carrier,[39] and they are stripped from the carrier by the energy from the inhalation. The release of respirable particles of the drug requires inspiration at relatively high flow (30–120 L/min).[39,40] A high inspiratory flow results in pharyngeal impaction of the larger carrier particles that compose the bulk of the aerosol. The oropharyngeal impaction and taste of carrier particles gives the patient the sensation of having inhaled a dose.

The internal geometry of the DPI device influences the resistance to inspiration and the inspiratory flow required to deaggregate and aerosolize the medication. Devices with higher resistance require a higher inspiratory flow to produce a dose. Inhalation through a high-resistance DPI may provide better drug delivery to the lower respiratory tract

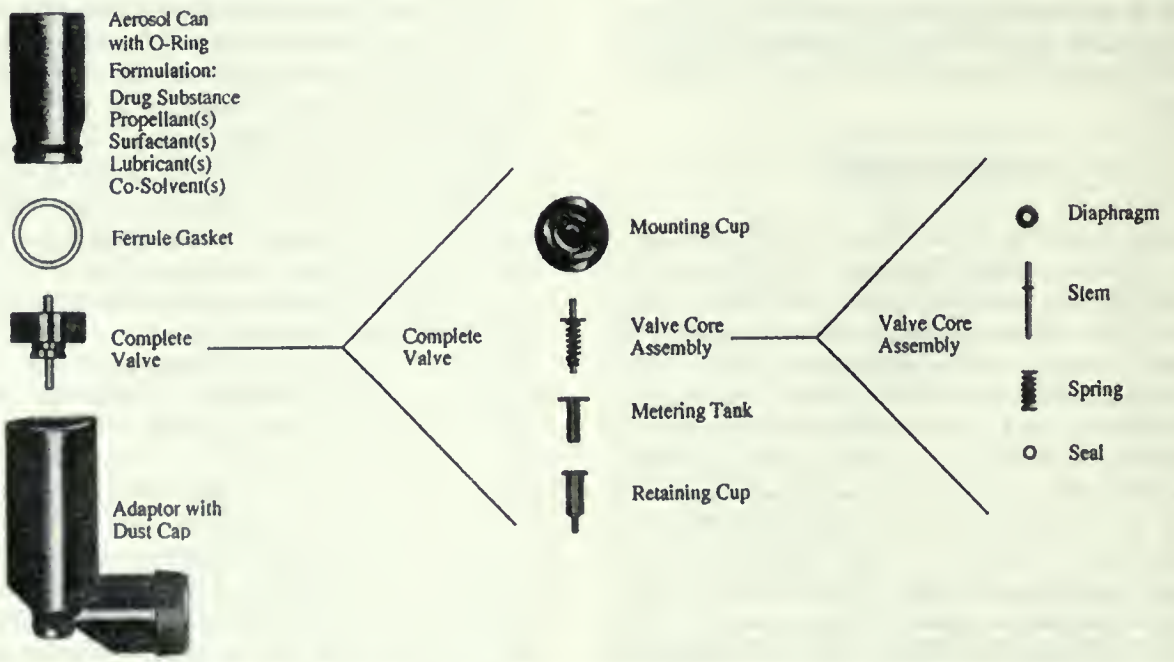

Fig. 9. Chlorofluorocarbon-free pressurized metered-dose inhaler assembly. (From Reference 1, with permission.)

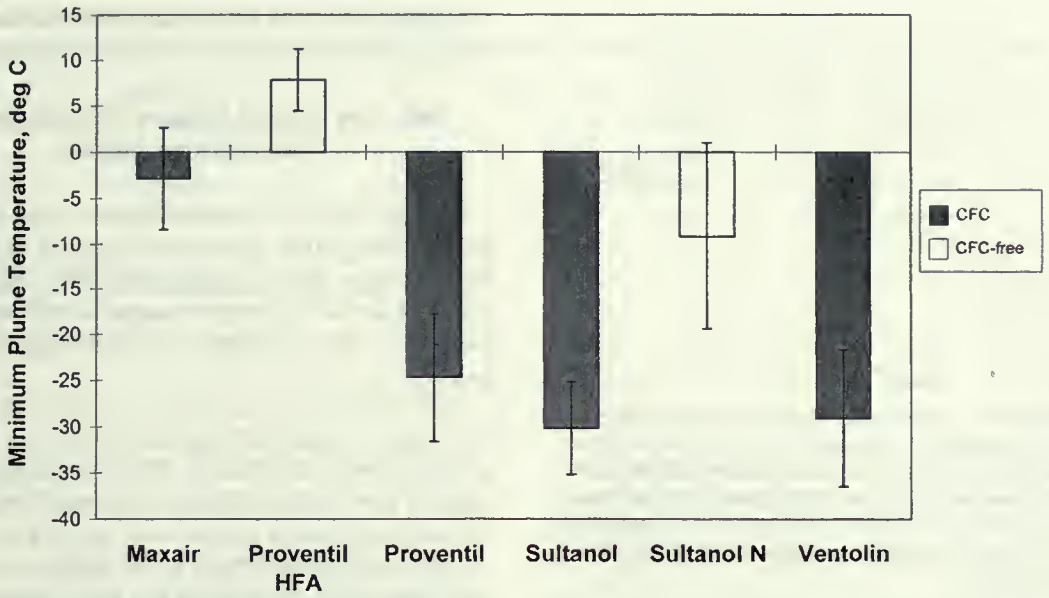

Fig. 10. The plume temperature of chlorofluorocarbon-propelled and chlorofluorocarbon-free albuterol pressurized metered-dose inhalers. Plume temperatures as low as –30° C have been associated with the cold-FREON effect. Only Proventil propelled by hydrofluoroalkane has a plume temperature greater than 5° C. (From Reference 1, with permission.)

than a pMDI[41,42] if the patient can reliably generate the required flow. High-resistance DPIs have not been shown to provide better lung deposition or bronchodilation than low-resistance DPIs.[43] DPIs with multiple components require correct assembly of the apparatus and/or priming of the device to ensure aerosolization of the dry powder.[44]

DPIs produce aerosols in which most of the drug particles are in the respirable range, with distribution of particle sizes differing significantly among various DPIs.[37] High ambient humidity produces clumping of the powder, which creates larger particles that are not as effectively aerosolized.[45] Humid air is less efficient than dry air at deaggregating particles of dry powder, so high ambient humidity increases the size of drug particles in the aerosol and may reduce drug delivery to the lung. Newer DPI devices contain individual doses more protected from humidity. Humidity can accumulate if the DPI is stored with the cap off, or from condensation if the device is brought from a very cold environment into a warmer area.

Inspiratory Flow

Since the energy from the patient's inspiratory flow disperses the drug powder, the magnitude and duration of the patient's inspiratory effort influences aerosol generation from a DPI.[46] Failure to perform inhalation at a sufficiently fast inspiratory flow reduces the dose of the drug emitted from a DPI[47] and increases the distribution of particle sizes within the aerosol, with a variety of devices. For example, the Diskus DPI delivers approximately 90% of the labeled dose at inspiratory flows of 30–90 L/min, whereas the dose delivered by the high-resistance Turbuhaler DPI is significantly lower at 30 L/min than at 90 L/min. Also, the variability between doses at different inspiratory flows is higher with the Turbuhaler.[48–51] Figure 7 shows the effect of two inspiratory flows (30 L/min and 55 L/min) when using a pMDI, breath-actuated pMDI, Rotahaler, Turbuhaler, and Diskhaler.[50] The peak inspiratory flow of children is limited, and associated with age, making it unlikely that a child less than 6 years old could reliably empty a DPI that requires a flow $>$ 50 L/min (Fig. 8).[52]

Active DPI delivery devices are under investigation. These use either a small motor and impeller or compressed gas propulsion to disperse the powder. Aerosol production and airway deposition with these devices is less influenced by the patient's inspiratory flow than existing DPIs, which rely solely on patient effort for aerosol production.

Breath coordination is also important when using DPIs. Exhalation into a DPI may blow the powder out of the device and reduce drug delivery. Moreover, the humidity in the exhaled air reduces subsequent aerosol generation from the DPI, so patients must be instructed not to exhale into a DPI.

DPIs are breath-actuated, which reduces the problem of coordinating inspiration with actuation. The technique of using DPIs differs in important respects from the technique for a pMDI. Although DPIs are easier to use than pMDIs, up to 25% of patients may use DPIs improperly.[53] DPIs are critically dependent on inspiratory air flow to

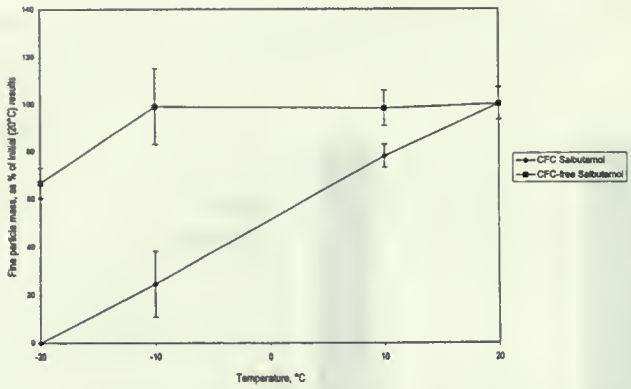

Fig. 11. Delivered fine particle mass versus temperature for chlorofluorocarbon-propelled albuterol and hydrofluoroalkane (HFA)-134a-propelled pressurized metered-dose inhalers (pMDIs). Compared to performance at 20° C, the chlorofluorocarbon-propelled pMDI delivers ≤ 74% at 10° C and < 23% at −10° C, whereas the HFA-propelled pMDI is unchanged down to −10° C. (From Reference 1, with permission.)

generate the aerosol, so they should be used with caution (if at all) in very young or ill children, weak patients, the elderly, or patients with altered mental status. Patients may need repeated instruction before they can master the technique of using a DPI, and periodic reassessment is necessary to ensure that patients continue to use optimal technique.[54] Clinicians must also learn the correct technique of using DPIs in order to train their patients in the use of these devices.

Although DPIs are widely used in Europe, where in some countries the use of CFC-propelled pMDIs was banned without exception, their acceptance in the United States has been less enthusiastic among both physicians and patients. Although DPIs and pMDIs have comparable clinical efficacy, projected DPI production and sales worldwide appear not to be more than 20% of the current pMDI market (personal communication, Glaxo Wellcome, 1999).

Why Dry Powder Inhalers Will Not Replace Metered-Dose Inhalers

Although DPIs are effective, they are more expensive to produce than pMDIs, making their use less likely in third-world markets. In the United States there continues to be a limited number of drugs available in DPI form, and no one device type is available with a full range of respiratory drugs.

More important is the degree to which drug delivery from many commercially available DPI systems is reduced in the presence of humidity. The high inspiratory flows required for optimal delivery have raised concerns about DPI effectiveness for patients with severe airway obstruction and children under age 6. In response to these concerns, the United States Food and Drug Administration is waiting for more pMDI replacements before lifting the current exemption for CFC-propelled pMDIs, delaying the target date for a complete ban on CFC use, established by the Montreal protocol.

Montreal Protocol

In 1987, the United Nations, with 144 signatory nations, called for a phase-out of CFCs and other environmentally-harmful gases. By 1996, the production of most CFCs had ceased in developed countries.[1,4] Exemption was made for CFC use in pMDIs for essential users. Phased exemption gave industry time to find alternative propellants. An International Pharmaceutical Aerosol Consortium for Toxicology was formed to find suitable alternatives.[2] This led to identification of HFA-134a, the first non-ozone-deplet-

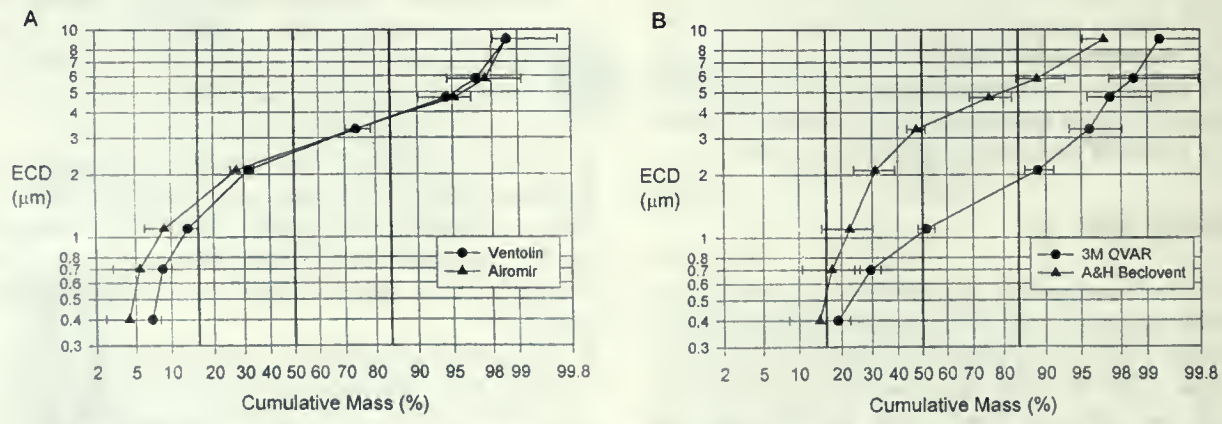

Fig. 12. Particle-size distributions from hydrofluoroalkane (HFA)-propelled pressurized metered-dose inhaler (pMDI) and from chlorofluorocarbon (CFC)-propelled pMDI. (A) Airomir (HFA) and Ventolin (CFC). (B) QVAR (HFA) and Beclovent (CFC). Measurements were made with an Anderson Cascade Impactor operated at 28.3 L/min. Cumulative mass (percent) refers to aerosolized drug that was deposited in an Anderson Cascade Impactor only. ECD = effective cut-off diameter. (From Reference 4, with permission.)

Table 6. Deposition of CFC- and HFA-Propelled BDP via pMDI

	Subjects (*n*)	Deposition* (nominal dose %)			
		Lungs	Oropharynx	Abdomen	Exhaled
CFC-BDP	Volunteers (9)	4 ± 3†	85 ± 20	9 ± 17	1 ± 1
HFA-BDP	Volunteers (3)	51 ± 12	29 ± 15	1 ± 2	18 ± 3
HFA-BDP	Asthmatics (16)	56 ± 9	31 ± 9	3 ± 4	9 ± 4

pMDI = pressurized metered-dose inhaler.
CFC = chlorofluorocarbon. BDP = beclomethasone dipropionate. HFA = hydrofluoroalkane.
*Deposition values are not corrected for tissue attenuation.
†Values represent means ± standard deviations.
(Adapted from Reference 55.)

ing pMDI propellant. Extensive toxicology and safety testing was conducted, which concluded that HFA-134a is at least as safe as CFC.

The first focus with the new propellant was on matching the performance characteristics of the CFC-propelled pMDI,[1] including drug concentration, metered volume, valve size, and pressure, to assure similar dose, similar particle size distribution, correct amount of fine particles < 4.7 μm, and dose reproducibility through the life of the pMDI. To achieve this, the pMDI valve, actuator, and formulation required modification.

Most widely-used CFC-propelled pMDIs are being reformulated as HFA-propelled pMDIs.[55] For the first time in 40 years, some manufacturers reevaluated performance of CFC-propelled pMDIs, addressing problems of inconsistent dosing, cold FREON effect, force of spray, and sensitivity of the pMDI to ambient temperature.

Airomir salbutamol sulfate (marketed in the United States as Proventil HFA) was the first HFA-propelled pMDI released with a new propellant and drug formulation (Table 5). This required substantial reengineering of key components, including the metering valve, elastome seals, smaller valve volume (25 μL), smaller actuator orifice, and wider mouthpiece orifice (Fig. 9).[1,56] The spray temperature is above freezing (14° C vs –2° C) (Fig. 10)[57] and the jetting force of the spray is reduced from 6.2 millinewtons to 2.4 millinewtons with the HFA device.[58] This reduced force and temperature drop at the plume was accompanied by less effect of temperature on performance (Fig. 11), providing more consistent and reliable performance than its CFC-propelled pMDI predecessor during winter, when canisters are cold.[55] While less temperature-dependent than the CFC formulations, deposition from the HFA-propelled pMDI is similarly reduced by humidity.

The CFC-propelled albuterol plume looks and sounds different than the HFA-propelled pMDI plume, because of lower jetting velocity.[4] Reformulation and hardware improvement improved canister performance with no reduction in dose per actuation when the inhaler is not used for hours or weeks, independent of orientation. The dose is consistent throughout the life of the canister, with less tail-off of drug when the canister is almost empty.[1] The particle size distributions of Airomir and Ventolin are similar (Fig. 12), with MMADs of 2.69 μm and 2.62 μm, respectively, but the respirable mass (< 5.8 μm) was 65.5% versus 41.4% ($p < 0.05$). However, the emitted dose of the HFA-propelled formulation is less.[4] With Airomir, the fine particle dose was higher with and comparable among several types and sizes of spacer.[59,60]

The transition to the HFA-propelled pMDI (eg, beclomethasone diproprionate and QVAR) has resulted in different formulations with different characteristics than the CFC-propelled formulations. Lack of a compatible surfactant required beclomethasone diproprionate to be dissolved in ethanol to make it soluble in HFA-34a, producing a solution rather than a suspension, as in CFC formulations.[55] Similar to the HFA-propelled albuterol pMDI, the plume force and temperature drop is less and storage stability better than the CFC-propelled Beclovent. While the emitted dose is similar (40.6 μg vs 45 μg), the particle distribution is substantially different—an MMAD of 1.07 μm versus 3.36 μm for the CFC-propelled formulation (see Fig. 12). These differences equate to better lung deposition and less oropharyngeal and abdominal deposi-

Table 7. Deposition of HFA-134a-Propelled Steroid from pMDI With and Without Spacer

HFA pMDI	Subjects, (*n*)	% Deposition	
		Lung	Oropharyx
BDP alone	normals (8)	51	29
BDP + Aerochamber		53	5
BDP + Volumatic		45	2
Flunisolide alone	normals (8)	23	60
Flunisolide + AeroHaler		41	15

pMDI = pressurized metered-dose inhaler
HFA = hydrofluoroalkane. pMDI = pressurized metered-dose inhaler.
BDP = beclomethasone dipropionate.
(Adapted from Reference 4.)

tion with the HFA-propelled formulation (Table 6). Lung deposition for HFA-propelled flunisolide was better and oropharyngeal deposition less with use of a valved holding chamber (Table 7).

Summary

Since 1956, the pMDI has become the most commonly prescribed and used aerosol device in the world. While concerns about global warming have led to a worldwide ban of CFCs, new HFA-propelled pMDIs are in development, requiring an evolutionary transition in the technology. The phase-out of CFC-propelled pMDIs has stimulated the development of more efficient DPIs, but issues such as cost of device production, inspiratory flow requirement, and the effects of ambient humidity on drug delivery may limit DPI acceptance, and industry projections suggest that the DPI will not completely replace the pMDI. Holding chambers may perform differently with HFA-propelled pMDIs, but HFA-propelled pMDIs generally appear to cause less oropharyngeal deposition and to improve lung delivery while continuing to provide protection from poor hand-breath coordination. The initial offerings of the emerging HFA-propelled pMDI technology appear to be resulting in an improved pMDI.

REFERENCES

1. Ross DL, Gabrio BJ. Advances in metered-dose inhaler technology with the development of chlorofluorocarbon-free drug delivery system. J Aerosol Med 1999;12:151–160.
2. Thiel CG. From Susie's question to CFC free: an inventor's perspective on forty years of MDI development and regulation. In: Dalby RN, Byron P, Farr SY, editors. Respiratory drug delivery V. Buffalo Grove: Interpharm Press; 1996: 115–123.
3. Molina MJ, Rowland FS. Stratospheric sink for chlorofluoromethanes: chlorine atom catalysed destruction of ozone. Nature 1974; 249:810–812.
4. Dolovich M. New delivery systems and propellants (review). Can Respir J 1999;6(3):290–295.
5. Fink JB, Dhand R. Aerosol therapy. In: Fink JB, Hunt G, editors. Clinical practice in respiratory care. Philadelphia: Lippincott Raven; 1998.
6. AARC Clinical Practice Guideline: Selection of an aerosol delivery device. Respir Care 1992;37(8):891–897.
7. Clark AR. MDIs: physics of aerosol formation. J Aerosol Med 1996;9 Suppl:S19–S26.
8. Dunbar CA, Watkins AP, Miler JF. An experimental investigation of the spray issued froma pMDI using laser diagnostic techniques. J Aerosol Med 1997;10(4):351–368.
9. Des Jardins T. Freon-propelled bronchodilator use as a potential hazard to asthmatic patients. Respir Care 1980;21(1)50–58.
10. Dolovich M. Physical principles underlying aerosol therapy. J Aerosol Med 1989:2(2);171–180.
11. Newhouse MT, Dolovich M. Aerosol therapy in children: basic mechanisms of pediatric respiratory disease: cellular and integrative. New York: BC Decker; 1991.
12. Breeden CC, Safirstein BH. Albuterol and spacer-induced atrial fibrillation. Chest 1990;98(3):762–763.
13. Silverglade A. Cardiac toxicity of aerosol propellants. JAMA 1972; 222(7);827–828.
14. Moren F. Aerosol dosage forms and formulations. In: Moren F, Newhouse MT, Dolovich MB, editors. Aerosols in medicine: principles, diagnosis and therapy. Amsterdam: Elsevier; 1985: 261–287.
15. Hallworth GW. The formulation and evaluation of pressurized metered-dose inhalers. In: Ganderton D, Jones T, editors. Drug delivery to the respiratory tract. Chichester, England: Ellis Horwood; 1987: 87–118.
16. Dhand R, Malik SK, Balakrishnan M, Verma SR. High speed photographic analysis of aerosols produced by metered-dose inhalers. J Pharm Pharmacol 1988;40(6):429–430.
17. Wiener MV. How to formulate aerosols to obtain the desired spray pattern. Soc Cos Chem 1958;9:289–297.
18. Newman SP. Aerosol generators and delivery systems. Respir Care 1991:36(9):939–951.
19. Larsen JS, Hahn M, Ekholm B, Wick KA. Evaluation of conventional press-and-breathe metered-dose inhaler technique in 501 patients. J Asthma 1994;31(3):193–199.
20. Guidry GG, Brown WD, Stogner SW, George RB. Incorrect use of metered-dose inhalers by medical personnel. Chest 1992;101(1):31–33.
21. Newman SP, Pavia D, Clarke SW. Simple instructions for using pressurized aerosol bronchodilators J R Soc Med 1980;73(11):776–779.
22. De Blaquiere P, Christensen DB, Carter WB, Martin TR. Use and misuse of metered-dose inhalers by patients with chronic lung disease: a controlled randomized trial of two instruction methods. Am Rev Respir Dis 1989;140(4):910–916.
23. Hampson NB, Mueller MP. Reduction in patient timing errors using a breath-activated metered-dose inhaler. Chest 1994;106(2):462–465.
24. Fink JB, Wilkes W, Dhand R, Fahey PJ, Tobin MJ. A new method to characterize the effects of spacers and holding chambers on poor hand-breath coordination during MDI use? (abstract) Respir Care 1998;43(10):873.
25. Salzman GA, Pyszczynski DR. Oropharyngeal candidiasis in patients treated with beclomethasone dipropionate delivered by metered-dose inhaler alone and with Aerochamber. J Allergy Clin Immunol 1988;81(2):424–428.
26. Toogood JH, Baskerville J, Jennings B, Lefcoe NM, Johansson SA. Use of spacer to facilitate inhaled corticosteroid treatment of asthma. Am Rev Respir Dis 1984;129(5):723–729.
27. Rubin BK. Pressurized metered-dose inhalers and holding chambers for inhaled glucocorticoid therapy in childhood asthma (letter). J Allergy Clin Immunol 1999;103(6):1224–1225.
28. Closa RM, Ceballos JM, Gomez-Papi A, Galiana AS, Gutierrez C, Marti-Henneber C. Efficacy of bronchodilators adminstered by nebulizers verus spacer devices in infants with acute wheezing. Pediatr Pulmonol 1998;26(5):344–348.
29. Williams JR, Bothner JP, Swanton RD. Delivery of albuterol in a pediatric emergency department. Pediatr Emerg Care 1996;12(4): 263–267.
30. Cunningham SJ, Crain EF. Reduction of morbidity in asthmatic children given a spacer device. Chest 1994;106(3):753–757.
31. Rau J, Zhu Y. Reservoir design and dose availability with long-term metered-dose inhaler corticosteroid use. J Aerosol Med 1998;11(1): 15–26.
32. Berg E. In vitro properties of pressurized metered-dose inhalers with and without spacer devices (review). J Aerosol Med 1995;8 Suppl 3:S3–S10; discussion S11.
33. Barry PW, O'Callaghan C. The effect of delay, multiple actuations and spacer static charge on the in vitro delivery of budesonide from the Nebuhaler. Br J Clin Pharmacol 1995;40(1):76–78.

34. O'Callaghan C, Lynch J, Cant M, Robertson C. Improvement in sodium cromoglycate delivery from a spacer device by use of an antistatic lining, immediate inhalation, and avoiding multiple actuations of drug. Thorax 1993;48(6):603–606.
35. O'Callaghan C. In vitro performance of plastic spacer devices (review). J Aerosol Med 1997;10 Suppl 1:S31–S35.
36. Pierart F, Wildhaber JH, Vrancken I, Devadason SG, Le Souef PN. Washing plastic spacers in household detergent reduces electrostatic charge and greatly improves delivery. Eur Respir J 1999;13(3):673–678.
37. Dhand R, Fink J. Dry powder inhalers (review). Respir Care 1999; 44(8):940–951.
38. Ganderton D. The generation of respirable clouds from coarse powder aggregates. J Biopharm Sci 1992;3:101–105.
39. Dolovich M, Rheim R, Rashid F, Coates G, Hill M, Bowen B. Measurement of the particle size and dosing characteristics of a radiolabelled albuterol-sulphate lactose blend used in the SPIROS dry powder inhaler. In: Dalby RN, Byron P, Farr SY, editors. Respiratory drug delivery V. Buffalo Grove: Interpharm Press; 1996: 332–335.
40. Engel T, Heinig JH, Madsen F, Nikander K. Peak inspiratory flow and inspiratory vital capacity of patients with asthma measured with and without a new dry-powder inhaler device (Turbuhaler). Eur Respir J 1990;3(9):1037–1041.
41. Pedersen S, Hansen OR, Fuglsang G. Influence of inspiratory flow rate upon the effect of a Turbuhaler. Arch Dis Child 1990;65(3): 308–310.
42. Thorsson L, Edsbacke S, Conradson TB. Lung deposition of budesonide from Turbuhaler is twice that from a pressurized metered-dose inhaler (P-MDI). Eur Respir J 1994;7(10):1839–1844.
43. Svartengren K, Lindestad PA, Svartengren M, Philipson K, Bylin G, Camner P. Added external resistance reduces oropharyngeal deposition and increases lung deposition of aerosol particles in asthmatics. Am J Respir Crit Care Med 1995;152(1):32–37.
44. Hill LS, Slater AL. A comparison of the performance of two modern multidose dry powder asthma inhalers. Respir Med 1998;92(1):105–110.
45. Rajkumari NJ, Byron PR, Dalby RN. Testing of dry powder aerosol formulations in different environmental conditions. Int J Pharmacol 1995;113:123–130.
46. Timsina MP, Martin GP, Van der Kolk H, Tushulzen E, Enthoben R. The effect of inhalation flow on the performance of a dry powder inhalation system. Int J Pharmacol 1992;81:199–203.
47. Hindle M, Byron PR. Dose emissions from marketed dry powder inhalers. Int J Pharmacol 1995;116:169–177.
48. Kim CS, Garcia L. Delivery characteristics of albuterol powder aerosol by rotahaler. J Aerosol Med 1993;6:199–211.
49. Bisgaard H, Ifversen M, Klug B, Stamstrup K, Sumby B. Inspiratory flow rate through the Diskus/Accuhaler inhaler and Turbuhaler inhaler in children with asthma. J Aerosol Med 1995;8:100
50. Smith KJ, Chang H-K, Brown KF. Influence of flow rate on aerosol particle size distributions from pressurized and breath-actuated inhalers. J Aerosol Med 1998;11(4):231–245.
51. Prime D, Grant AC, Slater AL, Woodhouse RN. A critical comparison of the dose delivery characteristics of four alternative inhalation devices delivering salbutamol: pressurized metered-dose inhaler, Diskus inhaler, Diskhaler inhaler, and Turbuhaler inhaler. J Aerosol Med 1999;12(2):75–84.
52. Pedersen S. Delivery options for inhaled therapy in children over the age of 6 years. J Aerosol Med 1997;10 Suppl 1:S41–S44.
53. Bisgaard H. Delivery options for inhaled therapy in children under the age of 6 years. J Aerosol Med 1997;10 Suppl 1:S37–S40.
54. Kesten S, Elias M, Cartier A, Chapman KR. Patient handling of a multidose dry powder inhalation device for albuterol. Chest 1994; 105(4):1077–1081.
55. Leach C. Enhanced drug delivery through reformulating MDIs with HFA propellants –drug deposition and its effect on preclinical and clinical programs. In: Dalby RN, Byron P, Farr SY, editors. Respiratory drug delivery V. Buffalo Grove: Interpharm Press; 1996.
56. Woodcock A. Continuing patient care with metered-dose inhalers. J Aerosol Med 1995;8 Suppl 2:S5–S10.
57. Jun D, Carlson S, Ross D. The effect of temperature on drug delivery characteristics of chlorofluorocarbon (CFC) and hydrofluoroalkane (HFA) metered-dose inhalers (MDIs). In: Dalby RN, Byron PR, Farr SJ, editors. Respiratory drug delivery V. Buffalo Grove: Interpharm Press; 1996: 354–356.
58. Dolovich M, Leach CL. Drug delivery devices and propellants, In: Busse W, Holgate S, editors. Asthma and rhinitis. Oxford: Blackwell Science; 1999.
59. Dubus JC, Rhem R, Dolovich M. In vitro characterization of salubtamol generic MDIs: delviery via small spacers (abstract). Eur Respir J 1998;12:65S.
60. Donnell D, Harrison LI, Ward S, Klinger NM, Ekholm BP, Cooper KM, et al. Acute safety of the CFC-free propellant HFA-134a from a pressurized metered-dose inhaler. Eur J Clin Pharmacol 1995; 48(6):473–477.

Special Problems in Aerosol Delivery: Artificial Airways

Rajiv Dhand MD

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Influence of Gas Density on Aerosol Deposition within the Endotracheal Tube
Summary

[Respir Care 2000;45(6):636–645] *Key words: intubation, mechanical ventilation, deposition, endotracheal tube, tracheostomy tube, nebulizer, metered-dose inhaler.*

Introduction

Intubation of the trachea is often required for effective mechanical ventilation. The provision of an artificial airway helps to maintain airway patency, prevent aspiration, and deliver high concentrations of oxygen. Moreover, cuffed artificial airways allow application of positive airway pressure and facilitate suctioning of the airways. Artificial airways may also be used for drug delivery either by instillation of drug solutions or by administration of drug aerosols. Aerosol therapy via artificial airways is a routine practice in mechanically ventilated patients.

Two types of artificial airways are commonly used for long-term airway management. Endotracheal tubes are preferred for initial airway management in most mechanically ventilated patients, and they are passed into the trachea through the mouth or nose. For patients requiring long-term mechanical ventilation, or in special circumstances that preclude the use of endotracheal tubes, a tracheostomy tube is passed through a surgically created stoma in the anterior wall of the trachea. Endotracheal and tracheostomy tubes each have some standard features, but a number of variations to this basic design are found among artificial airways used in clinical practice.[1]

The presence of an artificial airway influences extrathoracic dead space, air flow turbulence, and airway resistance. The normal extrathoracic dead space (~75 mL) is decreased by approximately 60 mL when a 25-cm-long endotracheal tube with an internal diameter of 8 mm is used.[2] The artificial airway is the narrowest portion of the ventilator circuit and thus the site of the highest resistance to air flow.

Figure 1 shows the relationship of the pressure drop across endotracheal tubes of various diameters with gas flow. The slope of the graph of pressure versus flow is the resistance. The dramatic rise in resistance at high flows is characteristic of turbulent air flow.[3] Under conditions of laminar air flow, airway resistance is proportional to $1/r^4$, where r is the radius of the airway, whereas it is proportional to $1/r^5$ when air flow is turbulent.[3] Thus, the resistance of a 6 mm internal diameter endotracheal tube is 4.2 times higher than that of an 8 mm internal diameter endotracheal tube. The narrow diameter of endotracheal tubes, compared to the normal upper airway, and the high inspiratory air flows typically employed during mechanical ventilation predispose to turbulent air flow and higher airway resistance in intubated than in nonintubated patients.

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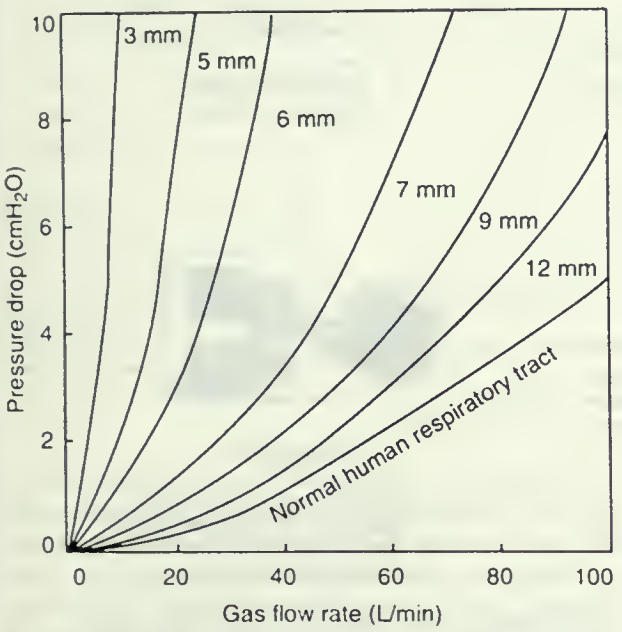

Fig. 1. Pressure drop across various sizes of endotracheal tube versus gas flow. (From Reference 3, with permission.)

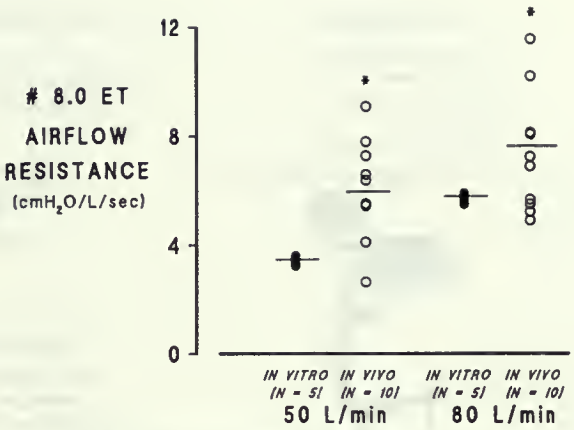

Fig. 2. Endotracheal tube resistance (average of inspiratory and expiratory resistance) at inspiratory flows of 50 and 80 L/min. The endotracheal tube resistance measured in vivo was higher than that measured in vitro, at both inspiratory flows. (From Reference 9, with permission.)

Both these factors are known to have a significant influence on aerosol deposition in the lung.

In spontaneously-breathing normal subjects, aerosol delivery to the lung is significantly lower at an inspiratory flow of 120 L/min than at 30 L/min.[4] Similarly, narrowing of the airways in patients with obstructive airways disease results in a greater aerosol deposition in the central airways.[5,6] In intubated, mechanically ventilated patients, endotracheal tubes produce significant airway resistance,[7] and the endotracheal tube resistance is dependent on inspiratory air flow.[8] Airway resistance due to endotracheal tubes in intubated patients may be higher than that measured in vitro with tubes of similar diameter.[9] Wright et al found that the mean air flow resistance with an endotracheal tube of internal diameter 8 mm was approximately 2.0–2.5 cm H_2O/L/s higher in vivo than the corresponding in vitro measurements (Fig. 2).[9] In view of the effects of an endotracheal tube on air flow resistance and turbulence, significant aerosol loss within the endotracheal tube is to be expected during mechanical ventilation.

MacIntyre et al found that only 2.9 ± 0.7% of nebulized ^{99m}technetium-labeled diethylenetriamine pentaacetic acid deposited in the lungs of mechanically ventilated patients,[10] whereas 1.6 ± 1.1% deposited in the distal 25–33% of the endotracheal tube. The values for pulmonary deposition were significantly lower than the values (10–14%) for pulmonary deposition reported for ambulatory patients.[11,12] On the basis of the ground-breaking study by MacIntyre et al, as well as other investigations, aerosol delivery in mechanically ventilated patients was thought to be significantly lower than in nonintubated patients.[13] The decreased efficiency of aerosol delivery during mechanical ventilation was largely attributed to the effects of the endotracheal tube, alluded to above. However, recent research has highlighted that several factors interact to influence aerosol deposition in intubated patients (Fig. 3).[14] The effects of aerosol deposition within artificial airways on aerosol delivery during mechanical ventilation need to be viewed in light of this new information.

Table 1 lists the factors that could influence aerosol deposition within artificial airways. One group of investigators who compared pulmonary deposition of ^{99m}technetium-labeled fenoterol administered via metered-dose inhaler (MDI) with spacer (4 puffs) found no difference in aerosol delivery between tracheostomy and endotracheal tubes (6.1 ± 2.8 vs 4.6 ± 3.0%, respectively, $p < 0.12$).[15] Although response to bronchodilators administered via endotracheal or tracheostomy tubes has not been directly compared, obvious differences have not been observed in clinical studies, and fewer patients are ventilated with tracheostomy tubes than with endotracheal tubes. Therefore, most of the data regarding the influence of artificial airways on aerosol delivery pertain to endotracheal tubes.

Factors Influencing Aerosol Delivery through Endotracheal Tubes

The characteristics of the tube and other factors that influence aerosol deposition in mechanically ventilated patients[14] interact in determining drug deposition within an artificial airway. Minimizing aerosol losses within artificial airways could lead to greater pulmonary deposition of drug in mechanically ventilated patients.

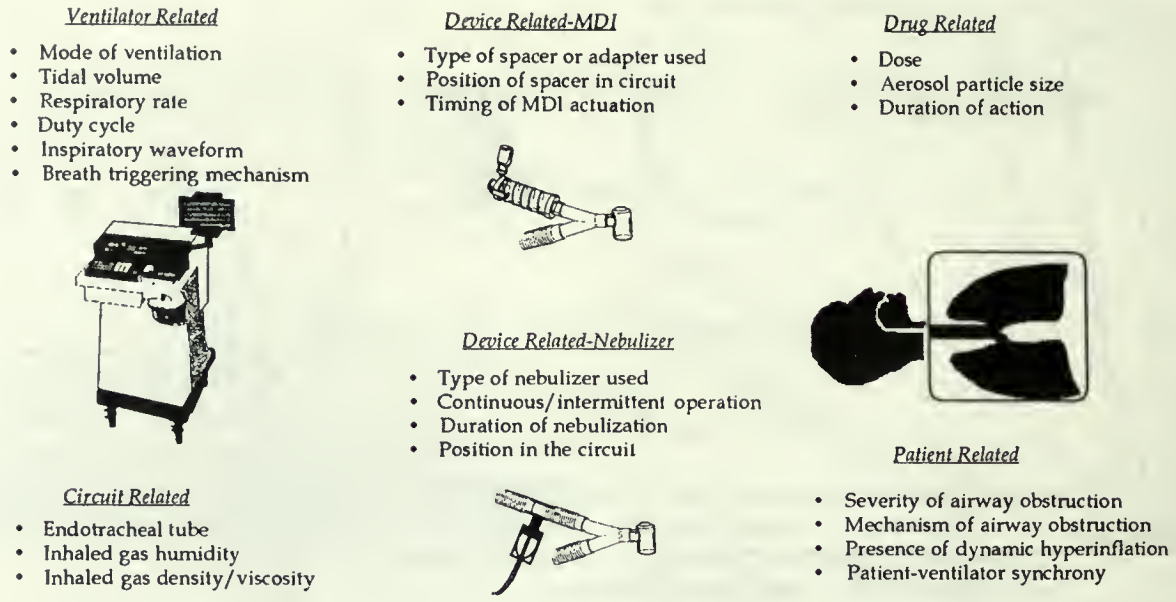

Fig. 3. Factors influencing aerosol deposition in mechanically ventilated patients. (From Reference 14, with permission.)

Endotracheal Tube Size

Several investigators have attempted to determine the influence of endotracheal tube size on aerosol delivery. Ahrens et al compared aerosol delivery with two nebulizers through endotracheal tubes of internal diameter 3, 6, and 9 mm.[16] They used continuous air flows (rather than cyclic flows) of 7.5, 10, 22.5, and 50 L/min through a simulated ventilator circuit. Table 2 summarizes their results with air flows of 22.5 and 50 L/min. This investigation is often quoted in support of the view that aerosol deposition is higher in endotracheal tubes of smaller diameter. However, it is obvious that the inspiratory air flow and particle distribution within the aerosol had a greater influence on aerosol delivery than the size of the endotracheal tube per se.

Another group of investigators identified several factors that influence aerosol delivery from nebulizers during mechanical ventilation.[17] They noted that aerosol delivery through an endotracheal tube of internal diameter 7 mm did not differ significantly from that observed with a 9 mm tube (Table 3). Once again, the type of nebulizer used had a much greater influence on aerosol delivery than the size of the endotracheal tube.[17] In an infant model of mechanical ventilation (endotracheal tube diameter 3.5 mm), 0.7 ± 0.1% and 0.4 ± 0.2% of the nominal dose placed in a nebulizer deposited in the endotracheal tube at inspiratory flows of 5 and 8 L/min, respectively, whereas the losses in the inspiratory tubing were 34.7 ± 0.7% and 43.7 ± 4.9%, respectively.[18]

Table 1. Factors Influencing Aerosol Deposition through Artificial Airways

Type: endotracheal or tracheostomy tube
Material: polyvinylchloride (PVC), silicone, or metal
Size
Electrostatic charge
Aerosol generator: metered-dose inhaler or nebulizer
Ventilator settings: tidal volume, breathing frequency, duty cycle
Ventilator circuit: humidity, temperature, density of inhaled gas

Table 2. Influence of Endotracheal Tube Size and Air Flow on Aerosol Delivery via Nebulizer

Device	Air Flow (L/min)	ET diameter (mm)	% Deposition* in ET	% Deposition* in Lung
Fan Jet†	22.5	3	10.3	8.8
		6	30.9	25.0
		9	25.0	54.4
	50	6	22.1	17.6
		9	19.1	30.9
Ultravent‡	22.5	3	14.7	76.5
		6	1.5	94.1
		9	0	99.0
	50	6	7.4	85.3
		9	1.5	92.6

ET = endotracheal tube
*Percent of nebulizer output (not nominal dose).
†Fan Jet mass median aerodynamic diameter = 3.95 μm.
‡Ultravent mass median aerodynamic diameter = 0.54 μm.
Nebulizers operated with flow of 7.5 L/min.
(Data from Reference 16.)

Table 3. Influence of Endotracheal Tube Size on Pulmonary Delivery and Aerosol Characteristics

Device	V_T (mL)	% Deposition*		MMAD (GSD)	
		ET (7 mm)	ET (9 mm)	ET (7 mm)	ET (9 mm)
Aerotech II	1,000	37	32	1.1 (1.6)†	1.1 (1.6)
	700	26	25	—	1.1 (1.6)†
Power Mist	1,000	—	11	1.3 (2.0)†	1.1 (1.7)
Twin Jet	1,000	18	—	—	0.6 (1.9)

*These are the highest/near highest values of "lung" delivery obtained with each device after operation for 20 minutes. Aerosol delivery was negligible with the Respirgard II.
MMAD = mass median aerodynamic diameter, GSD = geometric standard deviation, V_T = tidal volume, ET = endotracheal tube.
†Volume fill 3 mL; other tests with a volume fill of 2 mL.
Controlled mechanical ventilation: respiratory rate = 20 breaths/min, inspiratory flow = 40 L/min, ratio of inspiratory time to total time = 0.5, dry circuit.
(Data from Reference 17.)

With MDIs, one group of investigators found that differences in aerosol deposition depended on the size of the endotracheal tube,[19] whereas another group did not[20] (Table 4). Both groups of investigators used a swivel adapter connected to the endotracheal tube to actuate the MDI. Despite seemingly similar methods of aerosol delivery and analysis, significant differences in the delivery across 6 mm endotracheal tubes were observed (see Table 4). Clearly, the size of the endotracheal tube influences aerosol deposition, but the effect is variable, and other factors appear to have a greater impact on overall aerosol delivery.

Endotracheal Tube Material/Design

Endotracheal tubes may be made of polyvinylchloride (PVC) or silicone, whereas tracheostomy tubes are made of PVC, silicone, or silver. The material used to manufacture artificial airways is likely to alter aerosol deposition on the inner walls of the tube. However, to the best of my knowledge, the influence of the tube material/design on aerosol deposition within artificial airways has not been investigated.

Table 4. Influence of Endotracheal Tube Size on Aerosol Delivery with Metered-Dose Inhalers

Air Flow (L/min)	ET (mm)	% Deposition*	
		Filter	ET
30†	3	2.5	45.7
	5	10.7	43.7
	6	12.3	40.1
20‡	6	4.0	52.0
	9	10.0	30.0
60‡	6	5.0	57.0
	9	11.0	40.0

ET = endotracheal tube.
*Percent of nominal dose (by weight) of metaproterenol[19] or albuterol[20] administered with a swivel adapter connected to the ET. Metered-dose inhaler actuated into a continuous flow of air.
†Data from Reference 20.
‡Data from Reference 19.

Endotracheal Tube Electrostatic Charge

Artificial airways in common clinical use are made of PVC. These tubes are rigid initially, to facilitate insertion, but they become softer at body temperature. The electrostatic charge on the inner walls of PVC tubes attracts aerosol particles. Preliminary investigations in our laboratory (Fink JB, unpublished data, 2000) were carried out with albuterol delivered via MDI and cylindrical spacer (Aerovent) placed 15 cm from the endotracheal tube (the usual setup for administration of bronchodilator aerosols). Washing the endotracheal tube with soap increased aerosol delivery to the distal end of the endotracheal tube, compared to a dry tube (28.3 ± 1.6 vs 33.5 ± 1.0% of the nominal dose in dry and washed conditions, respectively). Reduction of electrostatic charge on the inner walls of the tube is expected to decrease aerosol deposition in the endotracheal tube, but this was not determined directly. Further investigations are needed to determine the extent of aerosol loss due to electrostatic charge within endotracheal tubes.

Aerosol Generator

The type of aerosol generator used, whether a nebulizer or MDI, influences aerosol delivery during mechanical ventilation.[21] Fuller et al administered 4 puffs of fenoterol radiolabeled with ^{99m}technetium pertechnate via MDI and cylindrical spacer placed in the inspiratory limb of the ventilator circuit of 7 patients. Another group of 9 patients were randomized to receive fenoterol solution containing ^{99m}technetium sulfur colloid. A Bennett Twin-jet nebulizer was used to nebulize the solution during the inspiratory phase, for a total of 15 minutes. Pulmonary deposition with the MDI and spacer (5.65 ± [SE] 1.1%) was significantly greater than that with the nebulizer (1.22 ± 0.4%).

Table 5. Aerosol Delivery from Nebulizers Versus Metered-Dose Inhalers with Holding Chambers

Device	Position (cm)	Radiolabel	% Deposition		Device
			Filter	ET	
MDI + large chamber	22	fenoterol with $^{99m}TcO_4$	30.3 ± 7.4	NA	NA
MDI + small chamber	22	fenoterol with $^{99m}TcO_4$	27.7 ± 5.1	5.9 ± 2.0	NA
Bennett nebulizer	70	^{99m}Tc-sulfur colloid in saline	4.6 ± 2.1*	2.3 ± 1.0	58.7 ± 9.6
Ultravent nebulizer	70	^{99m}Tc-sulfur colloid in saline	1.3 ± 0.4*	NA	80.9 ± 1.4

Values are means ± SD of 8–11 experiments.
ET = endotracheal tube. MDI = metered-dose inhaler. $^{99m}TcO_4$ = ^{99m}technetium pertechnate. NA = not available. ^{99m}Tc-sulfur = ^{99m}technetium-labeled sulfur colloid.
*$p < 0.05$, compared to MDI with chamber.
Controlled mechanical ventilation: tidal volume = 700 mL, respiratory rate = 12 breaths/min, inspiratory flow = 50 L/min, humidified circuit at 31–33°C, ET = 8 mm.
(Data from Reference 22.)

The absolute values for deposition reported in this study have been debated, but higher pulmonary deposition of aerosol with MDI and spacer than with jet nebulizer was corroborated by most subsequent investigations. For example, Fuller et al determined the amount of radioactivity depositing on a filter in a bench model of mechanical ventilation.[22] They found a significantly higher deposition of radioactivity on the filter with the MDI and spacer than with the nebulizer (Table 5). Moreover, the lower deposition with the nebulizer could not be explained by increased aerosol loss in the endotracheal tube. On the other hand, Diot et al reported equivalent delivery of albuterol aerosol with a jet nebulizer and MDI with spacer.[23] In a dry ventilator circuit, the amount of drug delivered with optimal use of an Aerotech II nebulizer was equal to that delivered by an MDI and cylindrical spacer. However, Marik et al found that the systemic bioavailability of albuterol delivered by an MDI and spacer to mechanically ventilated patients was 2.5 times higher than that observed with a jet nebulizer.[24] Since the endotracheal tube precludes gastrointestinal deposition in these patients, the quantity of drug recovered in the urine indirectly reflects its pulmonary deposition.

Therefore, at the present time, the consensus is that the MDI and spacer is more efficient than the jet nebulizer for aerosol delivery to mechanically ventilated patients. Both devices achieve comparable pulmonary drug delivery, because the dose of drug placed in the nebulizer is much higher than that administered by an MDI.

Endotracheal Tube Deposition of Aerosol from Metered-Dose Inhalers

The method of delivering aerosol with an MDI in a ventilator circuit influences the amount of aerosol depositing in the endotracheal tube and that delivered to the lower respiratory tract. Because of the complexity of studying aerosol deposition in mechanically ventilated patients, most studies were performed with bench models of mechanical ventilation. When the MDI canister was connected to the endotracheal tube with a swivel adapter, approximately 90% of the drug in the aerosol deposited in the adapter and endotracheal tube.[25] This amount could be significantly reduced by actuating the MDI in a reservoir, particularly by placing the reservoir at a distance from the endotracheal tube (Table 6).

Our investigations reveal that only a small fraction of the aerosol deposits in the endotracheal tube when the MDI is actuated into a spacer chamber in a dry ventilator circuit (Figs. 4 and 5).[26] In contrast, a higher proportion of aerosol is lost in the tube in a humidified ventilator circuit. Moreover, the amount of aerosol lost in the endotracheal tube with a hydrofluoroalkane-propelled MDI (12.4%) was similar to that with the chlorofluorocarbon-propelled MDI (12.9%), although the amount of drug exiting the spacer was significantly lower with the hydrofluoroalkane-propelled MDI than with the chlorofluorocarbon-propelled MDI (42.8 vs 60.5% in humid conditions, respectively) (see Figs. 4 and 5). Closer examination of these data reveal that similar amounts of drug entered the endotracheal tube

Table 6. Effect of the Placement of the MDI and Actuator on the Site of Aerosol Deposition

Method of Actuation	Site of Deposition	% Deposition*	
		Circuit	Filter
MDI on ET	Adapter and ET	92.7	7.3
MDI + spacer on ET	Spacer, circuit Y	67.2	32.1
	ET	0.7	
MDI + spacer in inspiratory limb	Spacer	65.2	29.0
	ET	5.9	

MDI = metered-dose inhaler.
ET = endotracheal tube.
*Percent of albuterol deposited at each site as a percent of the nominal dose.
Controlled mechanical ventilation: tidal volume = 800 mL, respiratory rate = 12 breaths/min, sine wave flow, dry circuit, ET = 8 mm.
(Data from Reference 25.)

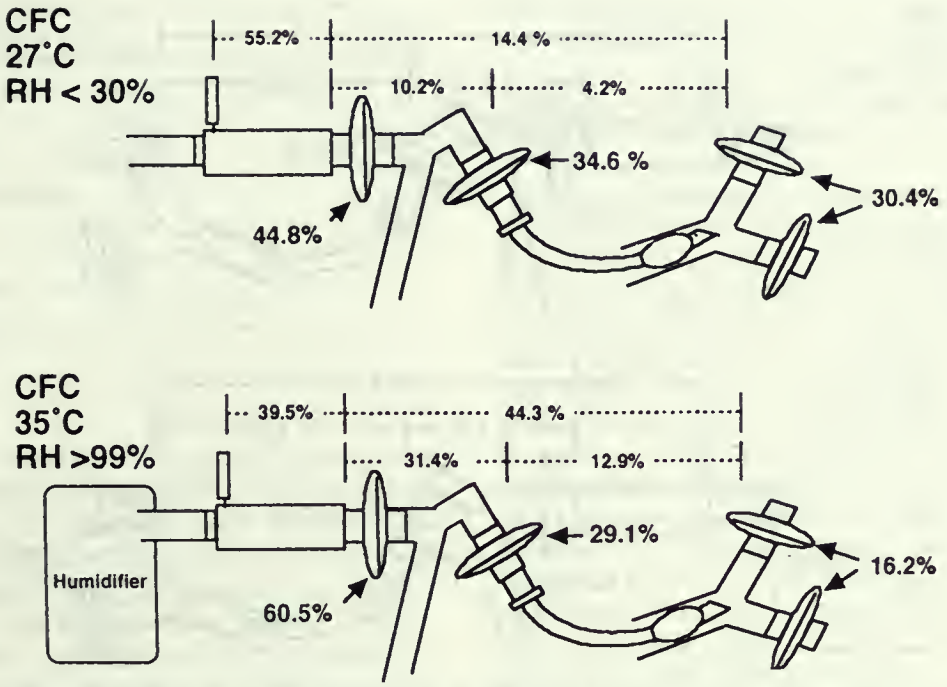

Fig. 4. Albuterol delivery, expressed as percent of the nominal dose, from a chlorofluorocarbon-propelled metered-dose inhaler was measured on filters placed distal to the spacer chamber, proximal to the endotracheal tube, and at the ends of the bronchi. Drug deposition in the spacer chamber, ventilator circuit, endotracheal tube, and tracheobronchial model was calculated under dry conditions (top panel) and humidified conditions (bottom panel). Aerosol deposition in the endotracheal tube was greater in humidified than in dry conditions (12.9% in humidified vs 4.2% in dry). (From Reference 26, with permission.)

in dry and humid conditions (34.6% and 29.1%, respectively). Therefore, aerosol loss in the endotracheal tube (4.2% in dry and 12.9% in humid conditions, a difference of ~8.5%) contributed significantly to the ~14% difference in aerosol delivery to filters placed at the ends of the bronchi (30.4% in dry and 16.2% in humidified circuits). These findings suggest that a significant proportion of the aerosol delivered by an MDI deposits within a humidified ventilator circuit. Methods to decrease aerosol loss within the ventilator circuit and endotracheal tube could substantially improve pulmonary deposition of aerosol given via MDI with spacer in mechanically ventilated patients.

Endotracheal Tube Deposition of Aerosol from Jet Nebulizers

The efficiency of aerosol generation differs among nebulizer brands.[17] Nebulizers may be operated continuously or only during the inspiratory phase (intermittent operation). Continuous aerosol generation requires a pressurized gas source (either a wall outlet, pressurized gas cylinder, or compressor), whereas intermittent operation requires a separate line to conduct inspiratory air flow from the ventilator to the nebulizer. The aerosol generated by the nebulizer is entrained in the gas flowing through the ventilator circuit. Although the gas flow provided by the ventilator during intermittent operation is similar to that during continuous operation, the driving pressure provided by most ventilators to the nebulizer (< 15 psi) is much lower than the pressure from compressed gas sources or wall outlets (> 50 psi). Reduction in driving pressure is likely to reduce the efficiency of aerosol generation by nebulizers and also to increase the distribution of aerosol particle size. Once a critical operating pressure is achieved, intermittent operation of nebulizers is more efficient for aerosol delivery than is continuous operation, because aerosol waste during the expiratory phase is minimized.[27] Similar to MDIs, placing the nebulizer at a distance from the endotracheal tube also enhances aerosol delivery.[27]

In contrast to MDIs, deposition of nebulized aerosol within endotracheal tubes is quite low. O'Doherty et al reported the effect of various ventilator settings on aerosol delivery with a System 22 Acorn jet nebulizer.[28] The fraction of aerosol depositing on a filter placed beyond the endotracheal tube varied from 5.4% to 17.4% of the nominal dose, but the differences in tube deposition ranged from 0.6% to 2.2% (Table 7). Similarly, placing the neb-

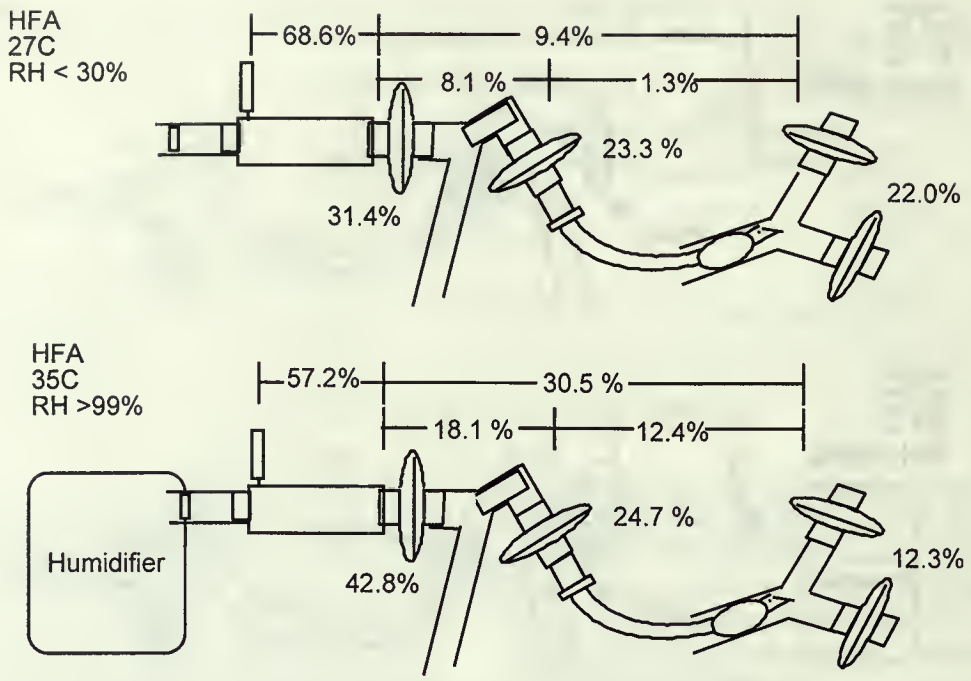

Fig. 5. Albuterol delivery, expressed as percent of the nominal dose, from a hydrofluoroalkane-propelled metered-dose inhaler was measured on filters placed distal to the spacer chamber, proximal to the endotracheal tube, and at the ends of the bronchi. Drug deposition in the spacer chamber, ventilator circuit, endotracheal tube, and tracheobronchial model was calculated under dry conditions (top panel) and humidified conditions (bottom panel). Aerosol deposition in the endotracheal tube was greater in humidified than in dry conditions (12.4% in humidified vs 1.3% in dry). (From Reference 26, with permission.)

ulizer close to the endotracheal tube produced minimal losses of aerosol within the endotracheal tube (Table 8).

Nebulization within a 600 mL spacer connected in the ventilator circuit increased pulmonary delivery of aerosol, despite a marginal increase in aerosol losses within the endotracheal tube (see Table 8). The in vitro observations were supported by subsequent investigations that showed a low (1–3% of nominal dose) deposition of nebulized aerosol within the trachea or endotracheal tube in mechanically ventilated patients.[29,30] The low deposition in the

Table 7. Effect of Ventilator Settings on Aerosol Delivery with a Nebulizer*

Ventilator Settings	$\dot{V}_E$ (L/min)	T_I (%)	Deposition %		MMAD
Rate (breaths/min)			Filter	Trachea/ET	
10	9	25	8.3 ± 0.8†	0.6 ± 0.1	2.99 ± 0.42
12	9	25	11.2 ± 1.6†	1.5 ± 0.1	3.02 ± 0.56
15‡	9	25	5.4 ± 0.2	1.9 ± 0.2	3.20 ± 0.40
15	6	25	9.9 ± 0.9†	2.2 ± 0.5	3.48 ± 0.20
15	12	25	5.8 ± 0.3	2.1 ± 0.5	3.34 ± 0.29
15	9	20	5.0 ± 0.8	2.1 ± 0.5	3.54 ± 0.30
15	9	33	13.3 ± 0.1†	2.2 ± 0.7	3.28 ± 0.20
15	9	50	17.4 ± 0.4†	1.9 ± 0.5	3.07 ± 0.19

*System 22 Acorn jet nebulizer; 3 mL fill volume, pause time 10%, ET 9 mm, ^{99m}technetium-HSA in water.
Values are expressed as mean ± standard error.
$\dot{V}_E$ = minute volume. T_I = inspiratory time, percent of total breath duration. ET = endotracheal tube. MMAD = mass median aerodynamic diameter.
†$p < 0.05$, compared to default setting.
‡Default setting.
(Data from Reference 28.)

Table 8. Effect of Nebulizer Position and Spacer on Aerosol Delivery via Nebulizer

Position	% Deposition	
	Filter	Trachea/ET
After circuit Y	5.4 ± 0.2	1.9 ± 0.2
Before circuit Y	8.0 ± 0.9	2.6 ± 1.4
With spacer*	10.3 ± 1.3	3.3 ± 0.7

Values are expressed as mean ± standard error.
ET = endotracheal tube.
*600 mL storage chamber placed in the inspiratory limb of the ventilator circuit.
(Data from Reference 28.)

endotracheal tube may reflect the low efficiency of aerosol generation by nebulizers or may be due to the experiments being conducted in dry ventilator circuits. However, careful examination of the pattern of aerosol deposition with nebulizers produced somewhat contradictory findings. O'Riordan et al used a mass balance technique to determine the deposition of nebulized aerosol at various sites in the ventilator circuit.[31] As shown in Table 9, approximately 10% of the nominal dose from a nebulizer deposited in the tracheostomy tube of mechanically ventilated patients, with the majority of the aerosol deposition occurring during the exhalation phase of the breathing cycle (~7%).[31] Since this is the only study that evaluated aerosol deposition in the artificial airway during exhalation, it is possible that a significant proportion of the aerosol inhaled, as determined by in vitro tests, is exhaled by the patient. Further investigations are needed to assess the extent of aerosol loss in the artificial airways during exhalation, and to develop methods to minimize this loss.

Endotracheal Tube Deposition of Aerosol with Ultrasonic Nebulizers

With ultrasonic nebulizers, a significant fraction of the aerosol generated deposits in the endotracheal tube.[32,33] The higher aerosol loss with the ultrasonic nebulizer than with the jet nebulizer occurs despite placement of the ultrasonic nebulizer at a distance of > 35 cm from the endotracheal tube (Table 10).[33]

Influence of Gas Density on Aerosol Deposition within the Endotracheal Tube

The use of helium-oxygen mixtures, which have lower gas density than air or oxygen, are believed to reduce air flow turbulence through narrowed airways. In previous studies using various helium-oxygen mixtures, Fink et al found that aerosol delivery via MDI showed a linear increase with the decrease in gas density within the ventilator circuit.[34] The use of an 80% helium-20% oxygen mixture in a dry ventilator circuit caused a 50% increase in the amount of drug delivered to the lower respiratory tract, compared to that observed with 100% oxygen (46.1 vs 30.4%, respectively) (unpublished data). The increase in aerosol delivery with the helium-oxygen mixture was accompanied by a decrease in aerosol deposition within the endotracheal tube. Therefore, mechanical ventilation with gas mixtures having lower density than air could reduce aerosol loss within artificial airways.

Summary

Several factors interact in influencing aerosol deposition during mechanical ventilation. Among these factors, the artificial airway is a significant barrier for aerosol deposition. Earlier studies overemphasized the impediments created by the artificial airway to aerosol delivery, because the aerosol generator was placed adjacent to the endotracheal tube or was connected to it. When the aerosol generator is placed away from the endotracheal tube, the fraction that deposits within the tube is reduced and greater aerosol deposition occurs in the lungs. The type of aerosol generator used and the ventilator settings have a greater effect than the size of the tube on the amount of aerosol that deposits in the artificial airway. To minimize aerosol loss within artificial airways, an endotracheal tube of the appropriate size should be selected. "Priming" the tube with a few doses of aerosol before use decreases the elec-

Table 9. Pattern of Deposition of Nebulized Aerosol During Mechanical Ventilation*

Inhalation Filter	Tracheostomy Tube			Expiratory Filter			Inhaled by Patient
	Total*	Inspiration	Exhalation	Total*	Leakage	Exhaled by Patient	
28.0 ± 6.0	9.6 ± 4.9	2.6 ± 0.5	7.0 ± 5.2	—	—	5.8 ± 5.4	15.3 ± 9.5

Values are means ± SE as a percent of the nominal dose of ^{99m}technetium-human serum albumin placed in the nebulizer.
The proportion of aerosol that bypassed the tube (leakage) to deposit on the exhalation filter was not stated.
*Determined during radiolabeled aerosol administration to patients; the remaining values were obtained by in vitro testing
Intermittent nebulization with Aerotech II placed 30 cm from the Y-piece: tidal volume = 500–1200 mL, respiratory rate = 10–16 breaths/min, ratio of inspiratory time to total time = 0.25 ± 0.09, dry circuit.
(Data from Reference 31.)

Table 10. Site of Deposition of Nebulized Aerosol during Mechanical Ventilation

Site of Deposition	% Deposition		
	Nebulizer*	Nebulizer + Spacer†	Ultrasonic‡
Lungs	2.3 ± 0.8	3.0 ± 0.8	5.3 ± 1.4
Trachea/ET	0.9 ± 0.5	1.5 ± 0.9	11.6 ± 3.9
Exhalation filter	11.1 ± 2.7	15.5 ± 1.5	7.5 ± 1.7
Nebulizer retention	51.5 ± 8.1	47.2 ± 1.0	29.6 ± 4.4
Unaccounted (in tubing)§	33.7 ± 9.0	30.7 ± 1.5	40.1 ± 3.5

Mean ± SD of values obtained in mechanically-ventilated patients.
ET = endotracheal tube.
*Data from Reference 29 (nebulizer at Y-piece).
†Data from Reference 30 (nebulizer 12 cm from Y-piece).
‡Data from Reference 33 (nebulizer 35 cm from Y-piece).
§Values are approximations.

trostatic charge on its walls and may reduce aerosol deposition within the tube. Similarly, using a spacer with the MDI, and placement of the combination in the inspiratory limb at a distance of at least 15 cm from the endotracheal tube reduces aerosol loss within the endotracheal tube. Use of nebulizers that produce submicronic aerosols, and placing them closer to the ventilator instead of closer to the patient also decreases aerosol impaction in the artificial airway. Use of a low inspiratory flow (30–60 L/min in adults), higher duty cycle (> 0.3), and helium-oxygen mixture instead of air or oxygen are other measures to reduce aerosol loss in the airway and thereby improve aerosol delivery to the lower respiratory tract of mechanically ventilated patients.

REFERENCES

1. Hess D, Branson R. Airway and suction equipment. In: Branson RD, Hess DR, Chatburn RL, editors. Respiratory care equipment, 2nd ed. Philadelphia: JB Lippincott; 1998: 157–186.
2. Nunn JF, Campbell EJM, Peckett BW. Anatomical subdivisions of the volume of the respiratory dead space and effect of position of the jaw. J Appl Physiol 1959;14:174–176.
3. Bishop MJ. Airway management. In: Tobin MJ, editor. Principles and practice of mechanical ventilation. New York: McGraw Hill; 1994; 695–710.
4. Ryan G, Dolovich MB, Obminski G, Cockcroft DW, Juniper E, Hargreave FE, Newhouse MT. Standardization of inhalation provocation tests: influence of nebulizer output, particle size, and method of inhalation. J Allergy Clin Immunol 1981;67(2):156–161.
5. Dolovich MB, Sanchis J, Rossman C, Newhouse MT. Aerosol penetrance: a sensitive index of peripheral airways obstruction. J Appl Physiol 1976;40(3):468–471.
6. Chan TL, Lippmann M. Experimental measurement and empirical modelling of the regional deposition of inhaled particles in humans. Am J Ind Hyg Assoc J 1980;41(6):399–409.
7. Gottfried SB, Higgs BD, Rossi A, Carli F, Mengeot PM, Calverly PMA, et al. Interrupter technique for measurement of respiratory mechanics in anesthetized humans. J Appl Physiol 1985;59(2):647–652.
8. Behrakis PK, Higgs BD, Baydur A, Zin WA, Milic-Emili J. Respiratory mechanics during halothane anesthesia and anesthesia-paralysis in humans. J Appl Physiol 1983;55(4):1085–1092.
9. Wright PE, Marini JJ, Bernard GR. In vitro versus in vivo comparison of endotracheal tube airflow resistance. Am Rev Respir Dis 1989;140(1):10–16.
10. MacIntyre NR, Silver RM, Miller CW, Schuler F, Coleman RE. Aerosol delivery in intubated, mechanically ventilated patients. Crit Care Med 1985;13(2):81–84.
11. Newman SP, Pavia D, Moren F, Sheahan NF, Clarke SW. Deposition of pressurized aerosols in the human respiratory tract. Thorax 1981;36(1):52–55.
12. Lewis RA, Fleming JS. Fractional deposition from a jet nebulizer: how it differs from a metered-dose inhaler. Br J Dis Chest 1985; 79(4):361–367.
13. Aerosol consensus statement. Consensus conference on aerosol delivery. Chest 1991;100(4):1106–1109.
14. Dhand R, Tobin MJ. Inhaled bronchodilator therapy in mechanically ventilated patients. Am J Respir Crit Care Med 1997;156(1):3–10.
15. Fuller H, Dolovich M, Turpie F, Posmituck G, Wong Pack W, Newhouse M. Aerosol deposition to the lungs by MDI in ventilated patients: endotracheal tubes vs tracheostomy (abstract). Chest 1990; 98(2 Suppl):27S.
16. Ahrens RC, Ries RA, Popendorf W, Wiese JA. The delivery of therapeutic aerosols through endotracheal tubes. Pediatr Pulmonol 1986;2(1):19–26.
17. O'Riordan TG, Greco MJ, Perry RJ, Smaldone GC. Nebulizer function during mechanical ventilation. Am Rev Respir Dis 1992;145(5): 1117–1122.
18. Coleman DM. Kelly HW, McWilliams BC. Determinants of aerosolized albuterol delivery to mechanically ventilated infants. Chest 1996;109(6):1607–1613.
19. Crogan SJ, Bishop MJ. Delivery efficiency of metered dose aerosols given via endotracheal tubes. Anesthesiology 1989;70(6):1008–1010.
20. Taylor RH, Lerman J. High-efficiency delivery of salbutamol with a metered-dose inhaler in narrow tracheal tubes and catheters. Anesthesiology 1991;74(2):360–363.
21. Fuller HD, Dolovich MB, Posmituck G, Pack WW, Newhouse MT. Pressurized aerosol versus jet aerosol delivery to mechanically ventilated patients: comparison of dose to the lungs. Am Rev Respir Dis 1990;141(2):440–444.
22. Fuller HD, Dolovich MB, Chambers C, Newhouse MT. Aerosol delivery during mechanical ventilation: a predicitve in vitro lung model. J Aerosol Med 1992;5:251–259.
23. Diot P, Morra L, Smaldone GC. Albuterol delivery in a model of mechanical ventilation: comparison of metered-dose inhaler and nebulizer efficiency. Am J Respir Crit Care Med 1995;152(4 pt 1):1391–1394.
24. Marik P, Hogan J, Krikorian J. A comparison of bronchodilator therapy delivered by nebulization and metered-dose inhaler in mechanically ventilated patients. Chest 1999;115(6):1653–1657.
25. Rau JL, Harwood RJ, Groff JL. Evaluation of a reservoir device for metered-dose bronchodilator delivery to intubated adults: an in vitro study. Chest 1992;102(3):924–930.
26. Fink JB, Dhand R, Grychowski J, Fahey PJ, Tobin MJ. Reconciling in vitro and in vivo measurements of aerosol delivery from a metered-dose inhaler during mechanical ventilation and defining efficiency-enhancing factors. Am J Respir Crit Care Med 1999;159(1): 63–68.
27. Hughes JM, Saez J. Effects of nebulizer mode and position in a mechanical ventilator circuit on dose effciency. Respir Care 1987; 32(12):1131–1135.

28. O'Doherty MJ, Thomas SHL, Page CJ, Treacher DF, Nunan TO. Delivery of a nebulized aerosol to a lung model during mechanical ventilation: effect of ventilator settings and nebulizer type, position, and volume of fill. Am Rev Respir Dis 1992;146(2):383–388.
29. Thomas SHL, O'Doherty MJ, Fidler HM, Page CJ, Treacher DF, Nunan TO. Pulmonary deposition of a nebulized aerosol during mechanical ventilation. Thorax 1993;48(2):154–159.
30. Harvey CJ, O'Doherty MJ, Page CJ, Thomas SHL, Nunan TO, Treacher DF. Effect of a spacer on pulmonary aerosol deposition-from a jet nebulizer during mechanical ventilation. Thorax 1995; 50(1):50–53.
31. O'Riordan TG, Palmer LB, Smaldone GC. Aerosol deposition in mechanically ventilated patients: optimizing nebulizer delivery. Am J Respir Crit Care Med 1994;149(1):214–219.
32. Thomas SHL, O'Doherty MJ, Page CJ, Treacher DF, Nunan TO. Delivery of ultrasonic nebulized aerosols to a lung model during mechancial ventilation. Am Rev Respir Dis 1993;148(4 Pt 1):872–877.
33. Harvey CJ, O'Doherty MJ, Page CJ, Thomas SHL, Nunan TO, Treacher DF. Comparison of jet and ultrasonic nebulizer pulmonary aerosol deposition during mechanical ventilation. Eur Respir J 1997; 10(4):905–909.
34. Fink J, Dhand R, Navin D, Fahey P, Tobin MJ. Heliox improves aerosol delivery from MDI during mechanical ventilation: an in vitro model (abstract). Am J Respir Crit Care Med 1997;155: A770.
35. Fink JB, Tobin MJ, Dhand R. Bronchodilator therapy in mechanically ventilated patients. Respir Care 1999;44(1):53–69.

Special Problems in Aerosol Delivery: Neonatal and Pediatric Considerations

Cynthia H Cole MD MPH

Introduction
Patient Considerations
Aerosol-System Considerations
Choosing an Aerosol Delivery System
Summary: Considerations for Improving Aerosol Delivery to Infants and Children

[Respir Care 2000;45(6):646–651] *Key words: aerosol, nebulizer, metered-dose inhaler, dry powder inhaler, pediatric, infant, neonate.*

Introduction

The importance of aerosol therapy in the management of respiratory disorders of pediatric patients has continued to increase over the past 15 years. This is due not only to an apparent increase in the occurrence of reactive airway disorders and greater utilization of aerosol therapy among pediatric patients with reactive airway disease,[1] but also to expanded applications for other clinical disorders, such as cystic fibrosis,[2] intervention for infectious processes,[3] and neonatal chronic lung disease (or bronchopulmonary dysplasia).[4–6] The breadth of clinical indications reflects the broader spectrum of pediatric patients utilizing aerosol therapy. Therefore, pediatric aerosol utilization encompasses patients as small as premature infants born at 24 weeks gestation (< 750 g birth weight) to adult-size teenagers. This diverse population, particularly premature neonates through young children, presents major challenges to effective, efficient aerosol therapy.[7–10] In addition to therapeutic incentives to deliver more effective therapy, there are economic and safety incentives, particularly for medications with lower safety profiles and higher cost.

The rationale and theoretical advantages of aerosol therapy are the same for pediatric patients as for adults: (1) to administer a lower dose of the medication, relative to that required for systemic therapy (in order to achieve a therapeutic effect with fewer systemic adverse effects) (2) direct delivery of the drug to the target organ, and (3) more rapid onset of action.[8,9] The goals of aerosol therapy include optimizing lung function and avoiding further lung damage.[10] These goals require careful, ongoing consideration of optimizing the benefit of the pulmonary status versus the acceptability of risks, especially in patients treated with inhaled steroid therapy.

The therapeutic efficacy of aerosolized medication for treating respiratory disorders depends upon delivery of adequate dose to the targeted sites within the lung. The primary factors influencing lung deposition include (1) aerosol particle size and the amount of respirable aerosol delivered, (2) the patient's breathing pattern and underlying disorder, (3) the aerosol delivery system and use of the delivery system.[8–10] Information regarding inhaled mass, lung deposition, and regional distribution of aerosolized medication is limited in neonates and young children. Data from in vitro models, animal studies, and in vivo infant studies indicate that aerosol delivery efficiency is lower and variability higher in infants and young children than in adults.[11–21] Aerosol delivery to a spontaneously-breathing adult with good inhalation technique is estimated to range from 10–25% of the nominal aerosol dose,[18] in contrast to 5–10% for a ventilated adult[19] and < 5% for a ventilated or spontaneously-breathing infant.[20] Fok et al found in vivo < 2% aerosol deposition by metered-dose inhaler

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(MDI) with spacer and jet nebulizer in spontaneously-breathing and ventilated infants with bronchopulmonary dysplasia.[21] Therefore, the precision, efficiency, and reproducibility of aerosol delivery to infants and children are limited by anatomical and physiologic factors, efficiency and use of aerosol delivery systems, and characteristics of the aerosol output.[8–10,20] Compensating for this inefficiency is often accomplished by increasing the nominal dose delivered in order to achieve a clinical effect. Therefore, special considerations relevant to infants and young children are required to optimize both aerosol delivery efficiency and therapeutic effect, and to minimize drug waste and adverse effects. This article reviews issues related to the infant and young pediatric patient.

Patient Considerations

Age-related patient considerations include anatomical, physiologic, and pathophysiologic considerations, as well as patient capability, cooperation, and compliance.[8–10,22] With respect to anatomical considerations, nasal breathing results in unpredictable loss of drug particles > 2 μm in diameter.[8] Therefore, the variable impact of nasal breathing must be considered among infants who are obligate nasal breathers and young children wearing face masks.[8–10,23] The smaller oropharynx reduces the amount of aerosol reaching the lower airways, as demonstrated in an in vitro comparison of replicas of an adult-size oropharynx and a child-size oropharynx, in which 35% of the nominal dose traversed the adult-size oropharynx, compared to 15% via the child-size oropharynx.[24] The mean airway lumen diameter from the main bronchi to respiratory bronchioli increases by 200–300% between birth and adulthood.[25] The smaller airway caliber of infants and children needs to be considered, since it may reduce aerosol delivery to the peripheral airways by favoring a more central pattern of deposition.[8,9,21] The small airway caliber can be further compromised by inflammation, edema, mucus, bronchoconstriction, and distorted airway growth and remodeling.[9] Aerosols with a greater proportion of fine particle fraction (< 3 μm) may negotiate the lower airways more effectively than aerosols with larger respirable size distribution. It is also important to be aware of the fact that postnatal alveolar development continues after birth through at least 2 years of age, with a disproportionate growth in lung volume relative to airways. The number of alveoli present at birth is estimated to be $20–150 \times 10^6$, compared to $300–600 \times 10^6$ in the adult. After alveolar development is complete, the alveoli continue to increase in size.[26] The normal growth and development of alveoli and airways after premature birth is often disrupted by assisted ventilation and neonatal chronic lung disease and its attendant fibrosis and remodeling. Therefore, acute and chronic lung disease may significantly affect the amount and pattern of aerosol deposition due to altered airway flow and atelectasis. In addition, postnatal systemic steroid therapy may contribute to abnormal pulmonary growth and development.[27] It is important to be aware of the ongoing pulmonary development so that adequate emphasis is given to achieving optimal therapeutic effect as early as possible in order to facilitate normal lung growth and development and to evaluate the effect of inhaled steroid therapy on developing lung. Inadequate therapy may result in life-long compromise in pulmonary development and function.

Two other major patient-related considerations include the highly variable breathing patterns and pulmonary mechanics of infants and children.[8–10,22] These physiologic considerations are among the primary determinants of aerosol deposition, and are greatly influenced by cooperation and underlying pathophysiology. The highly variable inspiratory flows are problematic for children of any age, but especially among crying infants, as it may result in decreased delivery to the lungs. The impact of variable inspiratory flow on the amount of respirable particle deposited in the lung depends on the extent of how high or low the flow, and also varies by aerosol device. For example, slower inspiratory flow is better for MDI, but maximum inspiratory flow is necessary for optimal dry powdered inhaler (DPI) performance in children capable of generating sufficient inspiratory flow. Among infants, the lower tidal volume (V_T), lower inspiratory flow, increased respiratory rate, and shorter breath-holding time decrease the dose delivered to the lungs.[8–10] A slower respiratory rate and appropriate inspiratory flow can improve aerosol deposition. Although low V_T is associated with lower dose delivery, and large, deep inspiratory volumes enhance deposition, recent evidence suggests that tidal breathing may result in similar benefit to slow, deep breaths with breath-holding.[28,29] Breath-holding appears to benefit deposition with MDIs and dosimetric nebulizers.[8] In addition to a patient's respiratory pattern, aerosol deposition is clearly affected by the type and severity of the underlying disease process with its attendant abnormal lung function and airway remodeling. Deposition may be heterogeneous and/or more central as obstructive airway disease progresses.[8–10,21,30]

Other patient-related considerations include a child's capability, compliance, and acceptance of aerosol therapy.[8–10,22] A child's capability to optimally utilize various aerosol generators and devices changes as he or she matures. Compliance and acceptance of aerosol delivery systems are additional challenges for young children because aerosol therapy requires preparation and maintenance, appropriate time to administer, cooperation, and correct technique by the operator and the child. These considerations are discussed further under selection of delivery system.

Aerosol-System Considerations

Aerosol-system considerations relate to factors that influence the amount of aerosol output and the characteristics of the aerosol output, such as particle size distribution. These "system" factors include medication formulation and concentration, the specific aerosol generator and aerosol delivery device, the interface between device and patient (ie, face mask, mouthpiece, or endotracheal tube), the operating conditions (eg, the driving gas flow), and the technique utilized by the operator and/or patient.[8–10,31]

Considerations regarding optimal aerosol particle size are similar for pediatric and adult patients in that it is preferable to have an aerosol particle size distribution that deposits in the lower respiratory tract. The optimal aerosol particle size is not known with certainty for infants and children. The range of 1–5 μm is often considered the range that has the greatest likelihood of depositing in small conducting airways and alveoli. It has been suggested that aerosol particles of 1–2 μm may provide the greatest lung dose to negotiate the small airways of infants. Finer particle size (< 3 μm) may be beneficial in nasal breathers and in children with obstructive airway disease. Therefore, it is important to consider the medication formulation and the aerosol system that will provide a greater fraction of particles within the desired aerosol particle size range.[8–10,31] Hydrofluoroalkane (HFA) reformulations of medications may favorably influence the aerosol particle size distribution, such as the HFA reformulation of beclomethasone.[32] However, many medications have not yet been reformulated with HFA propellants. Each reformulation will require evaluation regarding the effect of reformulation on aerosol particle behavior and size distribution.[33]

The available methods to aerosolize medications are nebulization (jet or ultrasonic), MDI, and breath-actuated DPI.[8,10,31] Numerous designs of each method are available, along with an increasing number of devices to facilitate aerosol delivery. Nebulization and pressurized MDIs with spacers are the two most effective options for infants and young children. DPI is a convenient aerosol method that uses micronized particles and contains no FREON propellant. However, since the efficiency and aerosol particle size of DPIs depend on rapid inspiration, their utilization has been limited to older children ($>$ 4–6 years old) who are capable of generating sufficiently rapid inspiratory flow ($\geq$ 30–120 L/min). New designs of DPIs with power-assisted flow that is independent of inspiratory flow may increase the number of children who can effectively utilize this method.[10,31,34–36]

Nebulization, by jet or ultrasonic nebulization, has been and continues to be a popular method to administer aerosol medications to infants and young children, despite the numerous factors that affect nebulized aerosol output and particle size.[7–11,14,15,31,37] Because of inefficient, highly variable output and poor reproducibility in aerosol particle size among different nebulizing devices, and even among devices of the same model, use of jet nebulization has shifted toward other alternatives, such as MDI with spacer, for infants and young children, and MDI with spacer or DPI for older children. The advantages of nebulization are that it can be used by patients of all ages and that it requires tidal breathing. It can also be administered intermittently or continuously over several hours, such as with high doses of β agonists delivered for prolonged periods.[38] Also, certain drugs can only be nebulized, such as antibiotics, surfactants, rhDNAse, and pentamidine. Advances in jet nebulizer technology may reduce their inefficiency and variability, improve the aerosol particle size, reduce medication waste, and reduce leakage of medication to the environment.[8–10,31] These modifications include improved designs, with breath-actuation dosimetry, entrainment of air via the nebulizing chamber, improved valves, and new plastics and molding techniques. Ultrasonic nebulization may have a higher aerosol output, slightly larger particle size distribution, and may minimize wastage of drug, compared to jet nebulization. Ultrasonic nebulization is not suitable for suspensions or viscous medications (such as antibiotics). Increased temperature of the fluid in ultrasonic nebulizers may denature protein solutions. A disadvantage of ultrasonic nebulization is that the equipment is expensive. Similar to jet nebulization, ultrasonic nebulization requires relatively more processing and maintenance than MDI with spacer or DPI, but if portability and performance are improved and if costs are contained, ultrasonic nebulizers may see increased use. Consideration of the patient interface with nebulization is important. Mouthpiece devices improve aerosol delivery by bypassing nasal filtration, but infants and young children may require a face mask during nebulization treatments. Close-fitting face masks with low-resistance exhalation valves and minimal dead space enhance aerosol delivery.[8–10,31]

MDIs dispense metered doses of micronized medication suspended in propellants along with surfactants. Use of the MDI alone is not appropriate for infants or young children because of the requirement to synchronize aerosol actuation with inhalation. Combining the MDI with a spacer or holding chamber lessens problems of coordinating actuation and inhalation, and decreases deposition of medication in the oropharynx due to reduction in aerosol velocity, inertial impaction, and selective removal of nonrespirable particles. The net effect is that aerosol output is increased, with improved delivery of respirable-size particles to smaller airways.[8–10,31]

MDI/spacer systems can be utilized for spontaneously-breathing infants with attached face mask, or with ventilated infants with the spacer connected in-line with the

ventilator circuit or directly attached to the endotracheal tube. The choice of spacer is an important consideration for infants and children, specifically with respect to the design, presence of low-resistance valves or no valves, volume, and electrostatic charge.[8–11,31,39–43] All the factors are critically important, since aerosol delivery efficiency varies among spacers, ventilatory variables, and conditions of use.[8–11,31]

There are 3 basic types of spacer: the open tube design, the reverse-flow design, and the holding chamber.[8–11,31,39–43] The two nonvalved spacers (open tube and reverse-flow) require some synchronization of inhalation with ventilation to minimize loss of aerosol.[8–10,31,42] Inhalation valves of spacers for infants or young children must have sufficiently low resistance to open readily with low inspiratory flow.[11,39,42] Although a one-way, low-resistance, valved holding chamber reduces loss of aerosol and allows the aerosol to be contained for a finite period of time until the child inhales, Fok et al recently found that nonvalved spacers are more effective than low-resistance valved spacers for aerosol delivery in spontaneously-breathing newborns and small infants.[40] These findings suggest that an MDI/spacer system with no low-resistance valve may actually deliver more aerosol to spontaneously-breathing infants. Further evaluation is needed of the benefit of low-resistance valves versus no valves in the context of ventilated or spontaneously-breathing neonatal/infant aerosol therapy.

The size of the spacer is important relative to aerosol concentration, particle impaction, and V_T.[8–11,31,41] Smaller-volume spacers result in greater aerosol concentration and particle impaction than larger volume spacers. The volume of the spacer should be appropriately low to facilitate the maximum amount of drug inhalation with a few inhalations for infants and children with low V_T (< 50 mL).[9,11,31,42]

Electrostatically charged plastic holding chambers reduce the total and respirable-size particle output because of the attraction of the electrostatically charged aerosol particles to the walls of the holding chamber.[44] The electrostatic charge of a holding chamber can be reduced by proper cleaning with a mild detergent, air drying, and priming the spacer with a thin surface of the aerosol prior to using the spacer. O'Callaghan et al demonstrated that application of an antistatic lining to the holding chamber increased total aerosolized cromolyn output five-fold and respirable-size particles two-fold, compared to the holding chamber without the antistatic lining.[44] The development of a nonelectrostatic holding chamber improved aerosol output by increasing the residence time of respirable-size particles and the availability of aerosol particles for inhalation.[45]

Incorrect and inconsistent use of an MDI/spacer system because of lack of understanding of factors that affect aerosol delivery or inattention to operating conditions can cause ineffectiveness, inefficiency, and greater variability in the dose delivery beyond the inherent differences in the MDI/spacer systems per se. Shaking the MDI suspension, priming the MDI metering valve with a few actuations before administering treatment, and avoiding rapid, multiple actuations are a few easy-to-control factors that can improve aerosol delivery for infants and young children. Immediate inhalation following actuation is important for optimizing aerosol delivery, but is not easy to control for spontaneously-breathing infants and children.[44,46] For ventilated infants and children, immediate manual or mechanical inhalation after actuation, along with attention to ventilatory variables (flow, V_T, inspiratory time), improve aerosol delivery and decrease variability.

The type of patient interface (eg, endotracheal tube, face mask, or mouthpiece) requires consideration.[11,31] Endotracheal tubes are choke points for reducing aerosol delivery.[47] Attention to endotracheal tube adapter design and aerosol particle size may lessen the impact of the endotracheal tube adapter. For young patients not capable of using mouthpieces, the face mask should be close-fitting, have minimal dead space, no holes for air entrainment, and low-resistance exhalation valves to enhance available aerosol without dilution and to minimize loss of aerosol.

Just as the breathing patterns and pulmonary mechanics of spontaneously-breathing infants and young children are important, close attention to operating conditions and ventilatory variables to ventilated patients is important. These considerations include attention to the placement of the MDI/spacer (in-line with ventilator circuit or attached to the endotracheal tube adapter), gas flow, V_T, peak and end-expiratory pressures, respiratory frequency, inspiratory time, and synchronization of actuation with inspiration.[8]

The MDI/spacer combination is convenient and can be utilized by patients of all ages, including ventilated and spontaneously-breathing premature infants. Treatment time with MDI/chamber combination is less than that with nebulization. Many MDI medications that are currently suspended in chlorofluorocarbon propellants are being reformulated to HFA propellants. Reformulation may alter the aerosol output and particle size for different medications. Knowledge of the aerosol output and particle size distribution of the specific medication and aerosol MDI/spacer system being utilized, and knowledge of the conditions under which the medication and system are tested are both necessary to make decisions regarding dosing and in assessing response.[32,33]

Choosing an Aerosol Delivery System

The choice of an aerosol delivery system for an infant or child is influenced by multiple factors, including the aero-

sol options that are available and feasible given the medication prescribed, the patient's capability of effectively utilizing the device, and what is affordable or reimbursable. Consideration of the drug to be aerosolized and the patient's age and capability are obvious starting points for choosing an aerosol delivery system. Premature and full-term newborns, infants, and children > 4–6 years of age can utilize MDI/spacer systems and nebulizers. Holding chambers that are approximately 150 mL appear to benefit infants with low V_T (< 50 mL). The low-resistance-valve holding chamber is currently the better option for delivery of inhaled steroids to infants and young children. Use of new hydrofluoroalkane-propelled MDI products (such as salbutamol and beclomethasone) may provide better aerosol particle size for deposition to the peripheral airways.[33] For children > 4–6 years old, MDI/spacer, nebulizer, and DPI are aerosol system options. Newer developments of DPIs with automatic-spacer devices, such as one developed with a breath-independent, mechanical actuation and a noneletrostatic spacer, may provide DPI aerosol options to younger children, since the new design requires no active cooperation and provides pure drug.[34]

Summary: Considerations for Improving Aerosol Delivery to Infants and Children

Identification of the determinants of efficient aerosol delivery and the specific challenges of aerosol delivery to infants and children can facilitate a systematic approach to optimize aerosol delivery to this population. There are inherent anatomical, physiologic, pathophysiologic, and technical limitations of aerosol efficiency in infants and young children. Nevertheless, one can enhance aerosol efficiency through application of sound principles of aerosol delivery and by exerting control over factors that are amenable to intervention. Improvements in aerosol formulations and delivery systems are being made that will enhance efficiency, decrease risk, and reduce waste and cost. Attention to aerosol particle size (1–3 μm mass median aerodynamic diameter and geometric standard deviation < 2 μm), and the concentration of this respirable particle fraction produced by an aerosol system may enhance delivery through endotracheal tubes and to the lower respiratory tract in infants and children with low V_T and low inspiratory rates. Attention to the choice of delivery system and to details of proper MDI technique (shaking, priming, immediate actuation, and avoiding multiple actuations prior to inhalation), choice of the aerosol spacer and patient interface (type of face mask, endotracheal tube, mouthpiece), spacer cleaning, and consideration of the medicine to be aerosolized (solution or suspension, viscosity) permit adjustment of the aerosol regimen to optimize delivery. All the patient-related, system-related, and operator-dependent considerations combined can greatly impact aerosol delivery efficacy and improve therapeutic response. Therefore, education and motivation of medical personnel, parents and caregivers, and patients regarding factors that influence aerosol efficiency and teaching of proper technique must be prioritized in order to improve aerosol delivery.

Aerosol therapy to all patients, especially infants and young children, would be well served if we had a clear understanding of the efficiency and functional differences among the various drugs and devices. These are substantive issues with daily therapeutic impact that have received increasingly outspoken concern over the past decade by aerosol scientists and clinicians.[7–10,22,31,33,48,49] These issues must be given due attention by drug and device manufacturers as well as by regulatory agencies. The medication, the device, and the conditions under which they are tested must be considered together and studied as thoroughly as the medications themselves with respect to total output and particle size distribution. As noted by Bisgaard,[10] medication dose recommendations are useless unless the device and technique used are specified. Medication dose recommendation could be facilitated by setting equivalent standards for generic and brand-name medications and devices. In addition, standardization of in vitro models with better replicas of infants' and children's anatomy (oropharynx, upper airways), and better in vitro lung models, plus utilization of realistic breathing patterns of infants and children will improve in vitro prediction of the in vivo dose delivered to lower airways. This would greatly facilitate selection of delivery systems under specific circumstances for infants and children of various ages.[9,10,31] Safety profile, therapeutic efficacy, and efficiency of aerosolized medications delivered to infants and children need to be rigorously studied. This is particularly true for medications with potentially great benefit but possible adverse effects, such as inhaled glucocorticoid therapy in extremely premature infants. Common sense, ethics, and due respect for the same high standard of approval requirements of adults and older children should motivate further research in understanding and improving aerosol delivery in infants and young children.

REFERENCES

1. Helms PJ, Christie G. Prospects for preventing asthma. Arch Dis Child. 1999;80(5):401–405.
2. Mukhopadhyay S, Singh M, Cater JI, Ogston S, Franklin M, Olver RE. Nebulised anti-pseudomonal antibiotic therapy in cystic fibrosis: a meta-analysis of benefits and risks. Thorax 1996;51(4)364–368.
3. Palmer LB, Smaldone GC, Simon SR, O'Riordan TG, Cuccia A. Aerosolized antibiotics in mechanically ventilated patients: delivery and response. Crit Care Med 1998;26(1):31–39.
4. Cole CH, Colton T, Shah BL, Abbasi S, MacKinnon BL, Demissie S, Frantz ID, III. Early inhaled glucocorticoid therapy to prevent bronchopulmonary dysplasia. N Engl J Med 1999;340(13):1005–1010.

5. Fok TF, Lam K, Dolovich M, Ng PC, Wong W, Cheung KL, So KW. Randomised controlled study of early use of inhaled corticosteroid in preterm infants with respiratory distress syndrome. Arch Dis Child Fetal Neonatal Ed 1999;80(3):F203–F208.
6. Arnon S, Grigg J, Silverman M. Effectiveness of budesonide aerosol in ventilator-dependent preterm babies: a preliminary report. Pediatr Pulmonol 1996;21(4):231–235.
7. Silverman M. Aerosol therapy in the newborn. Arch Dis Child 1990; 65(8)906–908.
8. Everard ML, Le Souef PN. Aerosol therapy and delivery systems. In: Taussig LM, Landau LI, editors. Pediatric respiratory medicine. St. Louis: Mosby; 1999: 286–299.
9. Dolovich M. Aerosol delivery to children: what to use, how to choose. Pediatr Pulmonol Suppl 1999;18:79–82.
10. Bisgaard H. Delivery of inhaled medications to children. J Asthma 1997;34(6):443–467.
11. Everard ML, Clark AR, Milner AD. Drug delivery from holding chambers with attached facemask. Arch Dis Child 1992;67(5):580–585.
12. Salmon B, Wilson NM, Silverman M. How much aerosol reaches the lungs of wheezy infants and toddlers? Arch Dis Child 1990;65(4): 401–403.
13. Watterberg KL, Clark AR, Kelly HW, Murphy S. Delivery of aerosolized medication to intubated babies. Pediatr Pulmonol 1991;10(2): 136–141.
14. Grigg J, Arnon S, Jones T, Clarke A, Silverman M. Delivery of therapeutic aerosols to intubated babies. Arch Dis Child 1992;67(1 Spec No):25–30.
15. Arnon S, Grigg J, Nikander K, Silverman M. Delivery of micronized budesonide suspension by metered dose inhaler and jet nebulizer into a neonatal ventilator circuit. Pediatr Pulmonol 1992;13(3):172–175.
16. O'Callaghan C, Hardy J, Stammers J, Stephenson TJ, Hull D. Evaluation of techniques for delivery of steroids to lungs of neonates using a rabbit model. Arch Dis Child 1992;67(1 Spec No):20–24.
17. Tal A, Golan H, Grauer N, Aviram M, Albin D, Quastel MR. Deposition pattern of radiolabeled salbutamol inhaled from a metered-dose inhaler by means of a spacer with mask in young children with airway obstruction. J Pediatr 1996;128(4):479–484.
18. Newhouse MT. Pulmonary drug targeting with aerosols: principles and clinical applications in adults and children. Am J Asthma Allergy Pediatr. 1993;7:23–25.
19. Fuller HD, Dolovich MB, Posmituck G. Pack WW, Newhouse MT. Pressurized aerosol versus jet aerosol delivery to mechanically ventilated patients: comparison of dose to the lungs. Am Rev Respir Dis 1990;141(2):440–444.
20. Newhouse MT, Dolovich M. Aerosol therapy in children. In: Chernick V, Mellins RB, editors. Basic mechanisms of pediatric respiratory disease: cellular and integrative. Philadelphia: Decker; 1991: 409–417.
21. Fok TF, Monkman S, Dolovich M, Gray S, Coates G, Paes B, et al. Efficiency of aerosol medication delivery from a metered dose inhaler versus jet nebulizer in infants with bronchopulmonary dysplasia. Pediatr Pulmonol 1996;21(5):301–309.
22. Gillies J. Overview of delivery system issues in pediatric asthma (review). Pediatr Pulmonol Suppl 1997;15:55–58.
23. Pedersen S, Ostergaard PA. Nasal inhalation as a cause of inefficient pulmonary aerosol inhalation technique in children. Allergy 1983; 38(3):191–194.
24. Olsson B. Aerosol particle generation from dry powder inhalers: can they equal pressurized metered dose inhalers? J Aerosol Med 1995; 8(Suppl 3):S13–S18; discussion S19.
25. Hislop AA, Haworth SG. Airway size and structure in the normal fetal and infant lung and the effect of premature delivery and artificial ventilation. Am Rev Respir Dis 1989;140(6):1717–1726.
26. Gaultier C. Developmental anatomy and physiology of the respiratory system systems in pediatric respiratory medicine. In: Taussig LM, Landau LI, editors. Pediatric respiratory medicine. St Louis: Mosby; 1999: 18–37.
27. Sahebjami H, Domino M. Effects of postnatal dexamethasone treatment on development of alveoli in adult rats. Exp Lung Res 1989; 15(6):961–973.
28. Gervais A, Begin P. Bronchodilation with a metered-dose inhaler plus an extension, using tidal breathing vs jet nebulization. Chest 1987;92(5):822–824.
29. Zainudin BM, Tolfree SEJ, Short M, Spiro SG. Influence of breathing pattern on lung deposition and bronchodilator response to nebulised salbutamol in patients with stable asthma. Thorax 1988;43(12): 987–991.
30. Alderson PO, Secker-Walker RH, Strominger DB, Markham J, Hill RL. Pulmonary deposition of aerosols in children with cystic fibrosis. J Pediatr 1974;84(4):479–484.
31. Dolovich M. Changing delivery methods for obstructive lung diseases (review). Curr Opin Pulm Med 1997;3(3):177–189.
32. Leach C. Enhanced drug delivery through reformulating MDIs with HFA propellant-drug deposition and its effect on preclinical and clinical programs. Proc Respir Drug Delivery V 1996;133–144.
33. Dolovich M. New delivery systems and propellants. Can Respir J 1999;6(3):290–295.
34. Bisgaard H. Automatic actuation of dry powder inhaler into a nonelectrostatic spacer. Am J Respir Crit Care Med 1998;157(2):518–521.
35. Devadason SG, Everard ML, MacEarlan C, Roller C, Summers QA, Swift P, et al. Lung deposition from the Turbuhaler in children with cystic fibrosis. Eur Respir J 1997;10(9):2023–2028.
36. Agertoft L, Pedersen S. Importance of the inhalation device on the effect of budesonide. Arch Dis Child 1993;69(1):130–133.
37. Hess D, Fisher D, Williams P, Pooler S, Kacmarek RM. Medication nebulizer performance: effects of diluent volume, nebulizer flow, and nebulizer brand. Chest 1996;110(2):498–505.
38. McPeck M, Tandon R, Hughes K, Smaldone GC. Aerosol delivery during continuous nebulization. Chest 1997;111(5):1200–1205.
39. Zainudin BMZ, Biddiscombe M, Tolfree SEJ, Short M, Spiro SG. Influence of size and inspiratory flow rates on the efficiency of a spacer: in vitro study (abstract). Thorax 1988;43(10):815P.
40. Fok TF, Lam K, Chan CK, Ng PC, Zhuang H, Wong W, Cheung KL. Aerosol delivery to non-ventilated infants by metered dose inhaler: should a valved spacer be used? Pediatr Pulmonol 1997;24(3):204–212.
41. Agertoft L, Pedersen S. Influence of spacer device on drug delivery to young children with asthma. Arch Dis Child 1994;71(3):217–219; discussion 219–220.
42. Dolovich M. Rationale for spacer use in children. Pediatr Pulmonol Suppl 1997;16:184–185.
43. Pedersen S. Inhalers and nebulizers: which to choose and why. Respir Med 1996;90(2):69–77.
44. O'Callaghan C, Lynch J, Cant M, Robertson C. Improvement in sodium cromoglycate delivery from a spacer device by use of an antistatic lining, immediate inhalation, and avoiding multiple actuations of drug. Thorax 1993;48(6):603–606.
45. Bisgaard H, Anhoj J, Klug B, Berg E. A non-electrostatic spacer for aerosol delivery. Arch Dis Child 1995;73(3):226–230.
46. Barry PW, Robertson CF, O'Callaghan C. Optimum use of a spacer device. Arch Dis Child. 1993;69(6):693–694.
47. Ahrens RC, Ries RA, Popendorf W, Wiese JA. Delivery of therapeutic aerosols through endotracheal tubes. Pediatr Pulmonol 1986; 2(1):19–26.
48. Smaldone GC. Aerosolized drug delivery in the 90s (editorial). Chest 1996;110(2):316–317.
49. Newhouse MT, Fuller HD. Rose is a rose is a rose? Aerosol therapy in ventilated patients: nebulizers versus metered dose inhalers: a continuing controversy (editorial). Am Rev Respir Dis 1993;148(6 Pt 1):1444–1446.

Drug Properties Affecting Aerosol Behavior

Sandra Suarez PhD and Anthony J Hickey PhD

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Summary

[Respir Care 2000;45(6):652–666] *Key words: aerosol, pulmonary deposition, pulmonary clearance, impaction, sedimentation, drug interaction.*

Introduction

Localized delivery of drugs to the respiratory tract has become an increasingly important and effective therapeutic method for treating a variety of pulmonary disorders, including asthma, bronchitis, and cystic fibrosis. Although the traditional form of inhalation therapy dates back to the earliest records of ancient cultures, the advantages of inhalation therapy have essentially remained the same. Several studies[1–3] have demonstrated the clinical advantage of inhalation aerosols over systemic therapy for the treatment of lung disorders. Relatively small doses are required for effective therapy, reducing systemic exposure to drug and thus minimizing adverse effects. Lower dosage regimens may provide considerable cost savings, especially with expensive therapeutic agents. Delivering small doses of active ingredients directly to the lung effectively targets the drug, thereby maximizing therapeutic effect while min-

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imizing adverse effects. On the other hand, the large surface area for absorption and the relatively low metabolic activity of the lungs[4,5] make this organ system a potential route for the systemic delivery of drugs that cannot be delivered by other means. Many studies have shown that the lungs provide substantially greater bioavailability for macromolecules than any other port of entry to the systemic circulation.[6,7]

The efficacy of a therapeutic aerosol is mainly determined by the amount of drug reaching the target site. The human lung has evolved to prevent the entry of atmospheric particulates. Therefore, unlike other routes of administration, delivering a known dose of drug to the site of action via inhalation requires a multidisciplinary scientific effort. Activities have focused on investigating both particle technology and drug delivery device technology as means of increasing the fraction of drug that reaches the periphery of the respiratory tract. Many studies have demonstrated that drug distribution and deposition along the respiratory tract depends on several factors: (1) characteristics of the inhaled formulation (particle diameter, size distribution, shape, electrical charge, density, and hygroscopicity),[8–10] (2) anatomy of the respiratory tract,[11] and (3) breathing patterns, such as frequency, tidal volume, and flow.[12–15] The ideal site of deposition along the airways for drugs intended for local delivery is not well understood. Because the location of autonomic receptors varies within the respiratory tract, successful therapy may depend on targeting specific receptor sites in the lung with different types of drugs.[16]

The rate of absorption from the periphery of the lung has been shown to be twice as fast as that taking place from the central portions, owing to the variable thickness of bronchial epithelial cells versus alveolar epithelial cells.[17] Therefore, to achieve maximum bioavailability of drugs aimed for systemic delivery, attention is required to deliver the drug to the periphery of the lungs. Drug residence time and, therefore, duration of effect at the site of action is a function of the rate of pulmonary clearance and pulmonary absorption, which in turn are determined by several factors, including the physicochemical properties of the drug, such as molecular weight, dissolution rate, partition coefficient, and charge.[12,18–21] An ideal inhalation aerosol for local delivery may be that for which the rate of pulmonary absorption and clearance are relatively slow. It has been observed that by increasing lipophilicity[22] and optimizing particle size (mass median aerodynamic diameter $< 5\ \mu m$)[12,23] and release rate[12,23,24] it is possible to increase the lung residence time of the drug. The therapeutic effect and the duration of this effect are determined not only by the drug dose and its pulmonary clearance, but also by drug-drug interactions. These interactions can take place at the level of drug-receptor binding (pharmacodynamic interaction) and/or during drug disposition (pharmacokinetic interactions: at the level of absorption, protein binding, and/or metabolism).

Numerous systems are available to deliver aerosols to the lungs. These include jet and ultrasonic nebulizers, propellant-driven metered-dose inhalers (pMDIs, pressurized canister), and dry powder inhalers (DPIs). The overall success of an aerosol delivery system is determined by its formulation components, the mechanism of dispersion, and patient compliance. In general, $< 20\%$ of the total drug in the inhaler device is delivered to the lower airways.[25] The challenges encountered with aerosol drug delivery include the control of particle size and distribution of the formulation and the reproducibility in dose uniformity.[26] Several studies have demonstrated the need for spacers and auxiliary devices to optimize the aerosol delivery from pMDIs.[27,28] However, adopting methods that increase the fraction deposited at the site of action might increase variability. It may be preferable to deliver smaller fractions of the dose reproducibility.

Delivery Devices

Inhaled therapeutic aerosols are generated by different devices (Fig. 1) that aim to deliver an aerosol to the lower airways. Inhalation devices can be classified into 3 categories: pMDIs, DPIs, and nebulizer inhalers.[29,30] Aerosol generators are characterized[31] using: (1) the output (mass of drug delivered per unit time), (2) the distribution of the agent in different aerodynamic size fractions, and (3) intra-device and inter-device reproducibility of operation.

Propellant-Driven Metered-Dose Inhalers

pMDIs are the most frequently prescribed aerosol delivery system because they are effective and convenient for a large proportion of patients. The fundamental components of pMDIs are an actuator, a metering valve, and a pressurized container that holds the micronized drug suspension or solution, propellant, and surfactant. The high vapor pressure propellant supplies the energy for dispersion in these delivery systems. The limitations of these devices are (1) poor coordination between actuation and inhalation by some patients,[32] and (2) the release of aerosol particles as large particles at a very high velocity (100 km/h). This results in a high oropharyngeal impaction of particles, with approximately 80% of the dose depositing in the oropharynx and only 10% in the pulmonary airways.[33]

To overcome the necessity for patient coordination usually required with these devices, breath-actuated pMDIs have been designed. These are essentially similar to conventional pMDIs, with the exception that the dose delivery is triggered by the patient's inspiratory flow.[34] The need of spacer and auxiliary devices for optimizing drug delivery

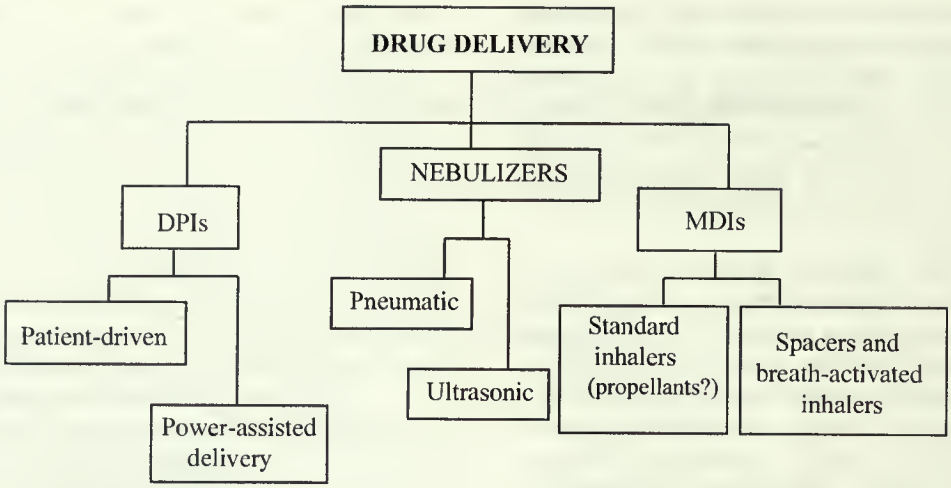

Fig. 1. Aerosol drug delivery devices. DPI = dry powder inhaler. MDI = metered-dose inhaler.

from pMDIs has been reported.[28,35] Attaching a spacer to the pMDI mouthpiece ensures that the emitted droplets become smaller and have reduced velocity before they are inhaled. The spacer acts as a holding chamber in which the large particles are filtered off, resulting in a reduction of the dose to the patient and impaction losses on the posterior wall of the oropharynx. Consequently, the dose deposited in the oropharynx by such devices is smaller, but the dose delivered to the pulmonary region is the same as or higher than that of a pMDI without a spacer.[36]

Dry Powder Inhalers

DPIs are the most recent development in respiratory therapy. The majority of these devices are breath-activated inhalers that rely on the patient's inspiratory flow to deaggregate and deliver the drug for inhalation, thereby eliminating the requirement of inhalation coordination inherent in pMDI use. However, with DPIs there is the need to generate at least moderate inspiratory flow in order to accomplish effective drug delivery. The drug in a DPI is in the form of a finely milled powder in large aggregates, either alone or in combination with some carrier substance, commonly lactose.[37] Most of the particles are initially too large to be carried into the lower airways, but the turbulent air stream created in the inhaler during inhalation causes the aggregates to break up into primary particles sufficiently small to be carried into the lower airways. Therefore, the deposition pattern depends on the inspiratory flow generated by the patient. A very low inspiratory flow is likely to move the dose from the inhaler into the patient's mouth, with very low deposition in the pulmonary airways. Shear, turbulence, and mechanical intervention may be used to aid in the dispersion of aerosols from dry powders.[38] Dry powder generation is often hindered by aggregation of the small particles,[39] which is in turn exacerbated by the hygroscopic nature of the drug[40] and its electrostatic charge. The reduction of powder hygroscopicity and electronic charge may enhance the future prospects of aerosol powder formulation.

Nebulizers

Nebulization is of increasing interest because it offers opportunities for novel techniques as well as providing a potential means of administration for aqueous formulations of biomolecules.[10] The most frequently used methods of nebulization are the air jet and ultrasonic devices.[41] The air jet nebulizer produces a stream of high air velocity that causes liquid to spray as a mist. Ultrasonic nebulizers utilize high frequencies to convert liquid into a fine mist.[34] A wide range of droplet size distributions are produced by both types of generators, depending on the brand, the operating conditions, and the composition of the liquid being nebulized.[41–43] Nebulizers produce smaller droplets than do pMDIs, and these smaller droplets penetrate more easily to the small airways.[34]

Mechanisms of Drug Deposition

Drugs for inhalation therapy are administered in aerosol form. An aerosol is defined as a suspension of liquid or solid in the form of fine particles dispersed in a gas. The ability of the aerosolized drug to reach the peripheral airways is a prerequisite for efficacy. Herein lies the fundamental problem of inhalation therapy, as the anatomy and physiology of the respiratory tract have evolved to prevent the entry of particulate matter. The regional pattern of deposition efficiency determines the specific pathways and rate at which deposited particles are ultimately cleared and

redistributed.[44] The pathology of disease of the lungs may considerably affect aerosol deposition. Patients with airway obstruction (eg, emphysema, asthma, chronic bronchitis) who inhaled radiolabeled aerosol showed increased central (tracheobronchial) deposition and diminished penetration to the peripheral pulmonary regions.[45]

The mechanisms by which particles deposit in the respiratory tract include impaction (inertial deposition), sedimentation (gravitational deposition), brownian diffusion, interception, and electrostatic precipitation.[44,46,47] The relative contribution of each depends on the characteristics of the inhaled particles, as well as on breathing patterns and respiratory tract anatomy. All mechanisms act simultaneously, but the first two mechanisms are most important for large-particle deposition within the airways (1 μm < MMAD < 10 μm). Diffusion, however, is the main determinant of deposition of smaller particles in peripheral regions of the lung.[48]

Impaction

Impaction occurs when a particle's momentum prevents it from changing course in an area where there is a change in the direction of bulk air flow. It is the main deposition mechanism in the upper airways, and at or near bronchial branching points. The probability of impaction increases with increasing air velocity, breathing frequency, and particle size.[9,44,46]

Sedimentation

Sedimentation results when the gravitational force acting on a particle overcomes the total force of the air resistance. Inspired particles will then fall out of the air stream at a constant rate.[49] This is an important mechanism in small airways having low air velocity. The probability of sedimentation is proportional to residence time in the airway and to particle size, and decreases with increasing breathing rate.

Diffusion

The collision of gas molecules with small aerosol particles exerts discrete nonuniform pressures at the particles' surfaces, resulting in random brownian motion. Thus, even in the absence of gravity, a particle in still air moves in a "random walk".[49] The effectiveness of brownian motion in depositing particles is inversely proportional to particle diameters of those particles < 0.5 μm,[50] and is important in bronchioles, alveoli, and at bronchial airway bifurcations. Molecule-size particles may deposit by diffusion in the upper respiratory tract, trachea, and larger bronchi.

Factors Controlling Respiratory Drug Deposition

The factors that control drug deposition are (1) characteristics of the inhaled particles, such as size, distribution, shape, electrical charge, density, and hygroscopicity, (2) anatomy of the respiratory tract, and (3) breathing patterns, such as frequency, tidal volume, and flow. Of these factors, aerosol particle size and size distribution are the most influential on aerosol deposition.

Particle Characteristics

The size of the particles is a critical factor affecting the site of their deposition, since it determines operating mechanisms and extent of penetration into the lungs.[51] Aerosol size is often expressed in terms of aerodynamic diameter (D_{ae}). The aerodynamic diameter is defined as the equivalent diameter of a spherical particle of unit density having the same settling velocity from an air stream as the particle in question.[9] Thus, particles that have higher than unit density will have actual diameters smaller than their D_{ae}. Conversely, particles with smaller than unit density will have geometric diameters larger than their D_{ae}. Aerosol size distributions may be characterized as practically monodisperse (uniform sizes, geometric standard deviation of < 1.2) or polydisperse (nonuniform sizes, geometric standard deviation ≥ 1.2).

In mammals, respiratory anatomy has evolved in such a way as to actively prevent inhalation of airborne particulates. The upper airways (nose, mouth, larynx, and pharynx) and the branching anatomy of the tracheobronchial tree act as a series of filters for inhaled particles. Thus, aerosol particles > 100 μm generally do not enter the respiratory tract and are trapped in the naso/oropharynx. Particles > 10 μm will not penetrate the tracheobronchial tree. Particles must generally be < 5 μm in order to reach the alveolar space.[6,49,51] On the other hand, particles < 0.5 μm in diameter penetrate the lung deeply, but have a high tendency to be exhaled without deposition. However, some studies have found that breath-holding can minimize expiration of small particles.[52,53]

Respiratory Tract Anatomy

Airway geometry affects particle deposition in various ways. For example, the diameter sets the necessary displacement by the particle before it contacts an airway surface, cross-section determines the air velocity for a given flow, and variations in diameter and branching patterns affect mixing between tidal and reserve air.[9] In contrast to many species of laboratory animal, humans have large lungs, a more symmetrical upper bronchial airway pattern, and are not obligate nose breathers. These anatomical differences produce greater amounts of upper bronchial par-

ticle deposition in humans.[11] In fact, large interspecies differences in the lung clearance of inhaled particles have been reported.[54–56] The interspecies variability in lung clearance may limit the applicability of animal models for particle-related diseases of the human bronchial upper airways. Thus, since the respiratory systems of animals and humans differ anatomically, differences in deposition patterns are also expected.

Respiratory Patterns

The pattern of respiration during aerosol exposure influences regional deposition, since breathing volume and frequency determine the mean flow rates in each region of the respiratory tract, which, in turn, influence the effectiveness of each deposition mechanism.[9,12,57,58] Turbulence tends to enhance particle deposition, the degree of potentiation depending on the particle size. Rapid breathing is often associated with increased deposition of larger particles in the upper respiratory tract, while slow, steady inhalation increases the number of particles that penetrate to the peripheral parts of the lungs.[59] Byron[12] proposed a mathematical model that identified the effect of particle size and breathing pattern on drug deposition. Slow breathing, with or without breath-holding, showed a broad maximum deposition in the ciliated airways (tracheobronchial region). The pulmonary maximum occurred between 1.5 μm and 2.5 μm with breath-holding and between 2.5 μm and 4 μm without breath-holding. Rapid inhalation showed similar trends: the tracheobronchial region maximum falls and shifts to between 3 μm and 6 μm. Pulmonary deposition sharpens and occurs between 1.5 μm and 2 μm with breath-holding, and between 2 μm and 3 μm without breath-holding.

When the above considerations are taken into account, the ideal scenario for aerosol would be: (1) aerosol $D_{ae} <$ 5 μm, to minimize oropharyngeal deposition, (2) slow, steady inhalation, and (3) a period of breath-holding on completion of inhalation.

Structure and Function of the Respiratory Tract

Assuming that an inhaled aerosol is successfully formulated and delivered in a reproducible dose to the lungs, attention should be given to the impact of respiratory structure and function on drug delivery. The following review briefly describes the important anatomical and histological features of the airways related to clearance of particulates.

The respiratory tract can be divided into upper and lower airways, with the line of division being the junction of the larynx and trachea.[60] The upper airways or nasopharyngeal region consists of the nose, mouth, larynx, and pharynx. Below the contours of the nasopharyngeal region, the lower airways resemble a series of tubes undergoing regular dichotomous branching.[61] Successive branching from the trachea to the alveoli reduces the diameter of the tubes, but markedly increases the surface area of the airways, which allows gas exchange[62,63] (Table 1). The lower airways can be divided into 3 physiologic zones: conducting, transitional, and respiratory zones.[48,61] The conducting zone consists of the larger tubes responsible for the bulk movement of air and blood. In the central airways, air flow is rapid and turbulent and no gas exchange occurs. The transitional zone plays a limited role in gas exchange. The characteristic "D" shape of the trachea is maintained by cartilage supported by smooth muscle fibers. The epithelial layer of the trachea and main bronchi is made up of several cell types, including ciliated, basal, and goblet. A large number of mucus-producing and serum-producing glands are located in the submucosa.

The human lung consists of 5 lobules and 10 bronchopulmonary segments. Arranged adjacent to each segment are lung lobules composed of 3–5 terminal bronchioles. Each bronchiole supplies the smallest structural unit of the lung, the acinus, which consists of alveolar ducts, alveolar sacs, and alveoli. At the level of small bronchi and bronchioles, the amount and organization of cartilage diminishes as the number of bronchial bifurcations increases. The acinus represents a marked change in morphology. The primary cells of the epithelium are the type I pneumocyte, which cover 90% of the entire alveolar surface. Type II pneumocytes are more numerous, but have a smaller total volume, and are responsible for the storage and secretion of lung surfactant. Less prevalent cell types include type III pneumocytes and alveolar macrophages. The alveolar blood barrier in its simplest form consists of a single epithelial cell, a basement membrane, and a single endothelial cell. While this morphologic arrangement readily facilitates the exchange, it can still represent a major barrier to large molecules. Before entering the systemic circulation, solutes must traverse a thin layer of fluid, the epithelial lining fluid. This layer tends to collect at the corners of the alveoli and is covered by an attenuated layer of surfactant. Unlike the larger airways, the alveolar region is lined with a surface active layer consisting of phospholipids (mainly phosphatidylcholine and phosphatidylglycerol)[64] and several key apoproteins, of which four have been identified (A, B, C, and D).[65] Apoprotein A is known to have a role in antibody recognition,[66] as well as on the enhancement of phagocytosis of particulates by alveolar macrophages.[67] The surfactant lining fluid plays an important role in maintaining alveolar fluid homeostasis and permeability, and participates in various defense mechanisms. Recent studies suggest that the surfactant may slow down diffusion out of the alveoli.[68,69]

The respiratory airways, from the upper airways to the terminal bronchioles, are lined with a viscoelastic, gel-like mucus layer 0.5–5.0 μm thick.[70] The secretion lining con-

Table 1. Schematic of Airway Branching in the Human Lung

Region		Generation	Diameter (mm)	Total Cross-Sectional Area (cm^2)	Cartilage	Nutrition Supply	Epithelial Cell Type
Conducting zone	Trachea	0	18	2.54	U-shaped	From the bronchial circulation	Columnar ciliated
	Main Bronchi	1	13	2.33			
	Lobar bronchi	2–3	7–5	2.13–2.0	Irregular shaped and helical plates		
	Segmental bronchi	4	4	2.48			
	Small bronchi	5–11	3–1	3.11			
	Bronchioles, terminal bronchioles	12–16	1.0–0.05	180	Absent		Cuboidal
Respiratory zone	Respiratory bronchioles	17–19	0.5	10^3		From the pulmonary circulation	Cuboidal to alveolar
	Alveolar ducts	20–22	0.3	—			Alveolar
	Alveolar sacs	23	0.3	10^4			

(Modified from Reference 63.)

sists of two layers: a fluid layer of low viscosity, which surrounds the cilia (periciliary fluid layer), and a more viscous layer on top, the mucus.[71] The mucus is a protective layer that consists of a complex mixture of glycoproteins released primarily by the goblet cells and local glands.[72] The mucus blanket removes inhaled particles from the airways by entrapment and mucociliary transport at a rate that depends on viscosity and elasticity.[11] There is evidence of neural control[73] and direct chemical control[74,75] on the release of mucus and, therefore, on the rate of mucus transport. The lung tissue is highly vascularized, which makes pulmonary targeting difficult because of fast absorption of most drugs (especially lipophilic and low-molecular-weight drugs).

Pulmonary Clearance

The primary function of the pulmonary defensive response to inhaled particles is to keep the respiratory surfaces of the alveoli clean and available for respiration. The elimination of particles deposited in the lower respiratory tract serves an important defense mechanism to prevent potentially adverse interactions of aerosols with lung cells. Insoluble particulates are cleared by several pathways, which are only partially understood. These pathways are known to be impaired in certain diseases and are thought to depend on the nature of the administered material.[15,76] Swallowing, expectoration, and coughing constitute the first sequence of clearance mechanisms operating in the naso/oropharynx and tracheobronchial tree. However, it has been suggested that the effect of cough may extend down to the level of the respiratory bronchioli, under conditions of excess mucus production.[77]

A major clearance mechanism for inhaled particulate matter deposited in the conducting airways is the mucociliary escalator, whereas uptake by alveolar macrophages[44,78] predominates in the alveolar region. In addition to these pathways, soluble particles can also be cleared by dissolution with subsequent absorption from the lower airways. The rate of particle clearance from these regions differs significantly and its prolongation can have serious consequences, causing lung diseases from the toxic effects of inhaled compounds. It is now well recognized that the lungs are a site for the uptake, accumulation, and/or metabolism of numerous endogenous or exogenous compounds. A number of reviews have covered several features of the metabolic functions of this organ.[79,80] Most of these studies focused on the role of pulmonary cytochrome P-450 isozymes. All metabolizing enzymes found in the liver are also found in the lung, although in smaller amounts. These include phase I reactive pulmonary cytochrome P-450 isozymes, flavin-containing mono-oxygenases, monoamine oxidase, aldehyde dehydrogenase, nicotinamide adenine dinucleotide phosphate (NADPH), cytochrome P-450 reductase, esterases, and epoxide hydrolase, and phase II conjugating enzymes such as N-acetyltransferase and sulfotransferase.

The rate at which a drug is cleared and absorbed from the respiratory tract (Fig. 2) depends on the dynamic interaction of several factors, predominantly: (1) the muco-

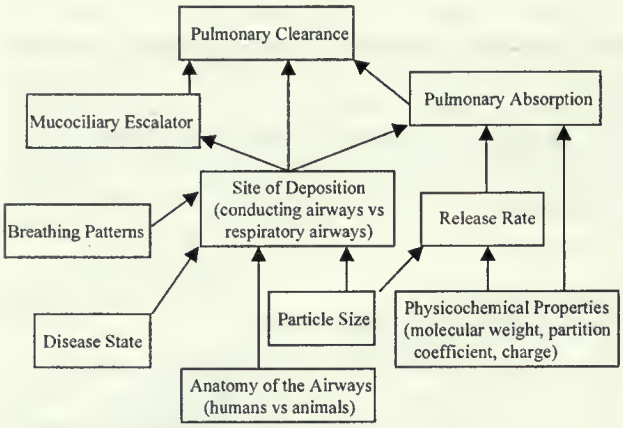

Fig. 2. Dynamic interaction of the factors affecting pulmonary clearance of inhaled drugs.

ciliary clearance rate, (2) site of deposition along the airways, (3) biopharmaceutical factors (particulates vs drug in solution), (4) drug release rate, and (5) the physicochemical properties of the drug, such as molecular weight, partition coefficient, and charge.

Mucociliary Clearance

Mucociliary clearance is a physiologic function of the respiratory tract to clear locally produced debris, excessive secretions, or unwanted inhaled particles. It consists of ciliated epithelial cells reaching from the naso/oropharynx and the upper tracheobronchial region down to the most peripheral terminal bronchioles. Beating of the cilia, together with mucus secreted by the goblet cells, contributes to an efficient clearance mechanism. The ciliary beat frequency is in the range of 1,000–1,200 beats/min.[11] Particles are transported at 5 mm/min if the effective stroke of a cilia is 5 μm and it beats at 1,000 beats/min. The normal mucociliary transport rates in humans are 5.5 mm/min in the trachea and 2.4 mm/min in the major bronchi.[81] The basal rate of Evans blue transport in healthy guinea pigs is 4.4 $\pm$ 0.02 mm/min.[82]

Mucociliary clearance kinetics are difficult to quantify. Studies of clearance kinetics usually involve administration of 3 μm (D_{ae}) insoluble iron oxide aerosols to normal humans. Byron[12] used a mathematical model to analyze the clearance data resulting from the administration of iron oxide. He and other investigators[83–85] have observed that 48.9% of the deposited material remained 24 hours after administration. However, recent studies using 6 μm insoluble particles administered to humans at an extremely low inhalation flow of 0.05 L/s (to ensure deposition in the small ciliated airways), showed that a large proportion of these particles were retained after 24 hours (20% cleared, with a clearance half-time of 2 d).[86]

For normal mucociliary clearance to occur it is necessary that the epithelial cells are intact, the ciliary activity and the rheology of mucus is normal, and that the depth and chemical composition of the periciliary fluid layer is optimal. Thus, the mucociliary escalator can be impaired by altering the volume of mucus secretion, the mucus viscosity and elasticity, or the ciliary beat frequency. Adrenergic agonists drugs such as salbutamol (albuterol)[82,87] have been reported to enhance clearance, whereas beclomethasone has no effect on mucociliary function.[88] Mucociliary clearance is known to be impaired in smokers,[89] in patients with chronic bronchitis,[76] and in acute asthmatics.[90] Certain diseases have the opposite effect—that of enhancing clearance rates.[91]

Pulmonary Endocytosis

Alveolar macrophages are considered the most important lung phagocytes. Macrophages are normal motile residents of the airways, interstitial matrix, and alveolar regions of the lungs.[92] They are plentiful in the lung, with a ratio of 1:8 with respect to Type 1 cells,[93] and their numbers and activity can increase substantially during inflammation or infection. Particles deposited in the alveolar region are taken up rapidly by macrophages. Phagocytic times of a few minutes[94] up to an hour[95] have been reported. The contribution of pulmonary endocytosis to the overall lung clearance is determined by the particle size and particle shape,[96] solubility, particle burden,[97,98] and the chemical nature of the inhaled aerosol. Alveolar macrophage-mediated clearance is a much slower process than mucociliary clearance, with retention half-times in the range of 50–80 days in rats and about 10 times longer in humans.[99] Particle phagocytosis by alveolar macrophages can be: (1) fast and efficient (eg, titanium dioxide, diameter $>$ 0.2 μm), (2) not efficient (eg, ultrafine particles), (3) incomplete (eg, long fibers cannot be completely phagocytized by a spherical cell with a diameter of approximately 12 μm), or (4) overloaded (ie, when particles occupy a large fraction of the volume of individual alveolar macrophages).[100] The long retention time of insoluble particles in the lungs can have serious consequences for pulmonary disease.

Alveolar macrophages can clear particles from the alveolar region in 4 ways: (1) transport along the alveolar surface to the mucociliary escalator, (2) internal enzymatic degradation, (3) translocation to the tracheobronchial lymph, and/or (4) combination of the interstitial lymphatic route and mucociliary transport (Fig. 3).

It is believed that translocation of particle-laden macrophages to the mucociliary region is responsible for the initial rapid clearance of insoluble particles in the first 24 hours after deposition.[101] However, transport of particles to the larynx by macrophages is relevant only in rodents

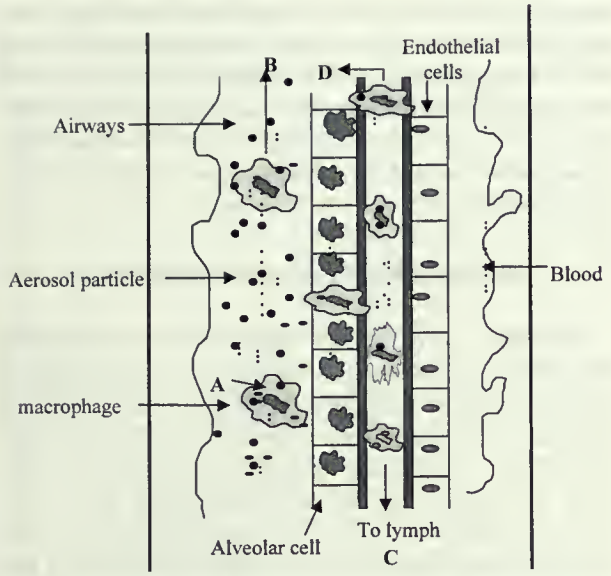

Fig. 3. Clearance pathways of particles by alveolar macrophages. A: Transport along the alveolar surface to the mucociliary transport. B: Internal enzymatic degradation. C: Translocation to the tracheobronchial lymph. D: Combination of the interstitial lymphatic route and mucociliary transport.

and is negligible in humans.[102] The initial transport rate of particles deposited in the lung periphery has been reported as 0.001–0.005 L/d, with exponential decline and a half-time of about 150 days.

Translocation of particles by alveolar macrophages to the lymph is known to contribute little to the overall clearance and to be determined by particle sizes higher than 3 μm[103] and particle burden.[104] A greater proportion (1.7%) of a dose of 3 μm particles were translocated to the lymph during a 128-day study, compared to 7 μm particles (0.2%), while no translocation was observed for 13 μm particles.[105] Ultrafine particles (20 nm) were translocated into the interstitium to a greater extent than larger particles.[106] Particles and particle-laden macrophages may be cleared from the alveolar region by translocation to the interstitium, with subsequent transport back to the airway epithelium surface (by an interconnecting pathway, namely, bronchus-associated lymphatic tissue), where they are cleared by the mucociliary escalator.[107] This interconnecting pathway has not become generally accepted because of a lack of satisfactory evidence.

The enzymatic activity following phagocytosis by alveolar macrophages is well known[108,109] and its contribution to the overall pulmonary clearance requires consideration for enzyme-sensitive compounds such as biomolecules. Lung surfactant may cause large molecules to aggregate, which could enhance ingestion and digestion by alveolar macrophages.[110]

Pulmonary Absorption

The main objectives of aerosol inhalation therapy have been to deliver the drug directly to the site of action and treat conditions within the tracheobronchial tree. However, the enormous absorptive surface area (approximately 100 m^2) of the alveolar epithelium and thin distal absorption surface (100–200 nm) make the lungs an attractive route for systemic delivery of drugs. Increasing interest in the lung as a route of delivery for systemic therapy has triggered detailed investigations of the mechanisms of drug absorption through the airways.

The mechanisms of absorption through the airways and the factors affecting this process have been investigated in detail.[110,111] However, the translocation of molecules from the apical to the basal side of the epithelium is a subject of controversy and speculation. Absorption through membranes may be classified in general as paracellular and transcellular. Several routes of absorption have been proposed: (1) transport via membrane pores, (2) vesicular transport (through type I and/or type II lung cells), and (3) transport via the intercellular tight junctions.

In general, small molecules can cross the membrane by diffusion[112] or by carrier-mediated transport.[113] A nonselective transport process like bulk flow through large pores or pinocytosis has also been postulated for the transport of small lipid-insoluble molecules.[114] In the case of macromolecules, it has been postulated that small peptides with molecular weight $<$ 40 kilodaltons (kDa) may be absorbed by paracellular transport, while for large molecules (molecular weight $>$ 40 kDa) transcytosis may be more important. There is evidence for receptor-mediated transport of some macromolecules, such as albumin.[115]

Transport Via Membrane Pores

Populations of mathematical "equivalent pores" have been derived in order to account for the different absorption characteristics of molecules throughout the pulmonary epithelium:[19,116] (1) small pores, which may represent the tight junctions or transcellular pores, have an estimated diameter of 1–5 nm;[117] (2) large pores, which may represent junctions between cells, vesicular transport, trijunctional complexes, or cellular defects, and may be responsible for the transport of molecules with diameters $>$ 5 nm; and (3) lipoid pores for the absorption of highly lipid-soluble compounds.[112] The existence of an ultra-large pore has also been proposed.[110]

Vesicular Transport (Transcytosis)

The mechanism that cells use to transport molecules across the membrane without disrupting the barrier function of the cell membrane or its electrochemical potential

is known as transcytosis.[118] The presence of vesicles within various epithelia has been demonstrated.[119,120] Absorptive transcytosis may be receptor-mediated (membrane receptors) or non-receptor-mediated. The latter can be classified as: (a) fluid phase (fluid phase non-receptor-mediated transcytosis), characterized by the presence of noncoated vesicles called caveolae, or (b) adsorptive transcytosis. Although there has been extensive research to elucidate fluid phase transcytosis, there is not enough evidence to support the role of this pathway in the transport of molecules across the pulmonary epithelium.[110]

The transcytosis of some antibodies is mediated by receptors on the plasma membrane, receptor-ligand complexes are localized into clathrin-coated pits, and the complex is internalized and moved across the cell or delivered to lysosomes.[110] Investigators have presented evidence for the existence of the albumin receptor on the alveolar epithelium.[121] Some proteins, such as caveolin, albondin (a 22 kDa integral membrane protein), albumin receptor, molecular chaperones, and an inositol triphosphate receptor are known to be transported into noncoated vesicles with opening diameters of approximately 40 nm.[122,123] Whether receptor-mediated or not, transcytosis seems to be relatively slow. It takes hours to days to be completed for molecules with molecular weight $>$ 40 kDa.[124]

Transport Via Tight Junctions

Tight junctions between the epithelial cells regulate the movement of small solutes, fluid, and ions. The importance of tight junctions in the transport of proteins is controversial.[111] Tight junctions are known to be complex structures of multiple proteins, which serve as intricate and dynamic fasteners of cells to each other. The coupling zones enable adjacent cells to communicate metabolically and electronically and may endow mechanical support.[125] The tightness or leakiness of the tight junctions may correlate with the number and continuity of rows or strands in the junctional web. The endothelial tight junctions' structure and integrity differ from that of the epithelial tight junctions. The endothelium is known to be more permeable to macromolecules than the epithelium, and may not limit the protein absorption from the airways.[126] Some investigators[127] have reported that increasing intravascular pressure results in horseradish peroxidase moving through the junctions of the endothelial cells, but movement into the alveoli is blocked by the interepithelial junctions. The tightest endothelial junctions are seen in the arterioles and consist of 3–6 interconnected rows of particles and only rare discontinuities. The most tenuous junctions are seen in the venular endothelial cells, which are known to line the walls of the leakiest portion of the vascular system. Polypeptides of at least 12 kDa (3–4 nm in diameter) may pass into the interstitium via the endothelial tight junctions.[128] The substructure of a normal epithelial tight junction exhibits a series of 3–6 interconnecting ridges that run belt-like around the cells.[129] The majority of the equivalent pore studies of pulmonary epithelium suggest that the small pores possess openings with diameters of 0.5–2 nm at the apical surface, and this prohibits passage of most water-soluble solutes.[129]

Factors Affecting Absorption Kinetics

The effects of molecular weight, partition coefficient, pH, release rate, interspecies variability, and osmolarity on absorption kinetics have been studied in detail. Enna and Schanker[19] examined the absorption of saccharides and urea of various molecular weights, and found that the first-order rate constant (k) decreased with increasing molecular weight. Because of the low lipid solubility of these hydrophilic compounds, these investigators proposed that absorption occurred through aqueous channels of intercellular spaces in the lipid membrane. In another study it was found that those compounds with molecular weight $<$ 1,000 Da were absorbed at faster rates (half-time = 90 min) than the larger molecules (half-time = 3–27 h).[17] Solutes with molecular weights in the range of 100–1,000 Da are absorbed with half-times of 8–40 minutes.[18]

Once droplets containing drugs enter the fluid within the air spaces, they rapidly diffuse into the surrounding medium. The rate of clearance from the fluid lining the air spaces can be predicted using the following equation:[130]

$$\frac{dQ}{dt} = -PS\Delta c$$

where Q is the quantity of drug in the air space, t is time, P is the permeability of the blood-gas barrier, S is the surface area of the barrier, and Δc is the concentration gradient across the barrier.

Some studies have reported that solutes penetrate the alveolar wall at rates that increase with the lipid solubility of the compound.[20,131,132] Those compounds having partition coefficients $>$ 108 are absorbed rapidly. However, there appears to be no continuity for others with partition coefficients $<$ 106.[20] Lipid-soluble compounds are absorbed more rapidly than lipid-insoluble compounds, which cross the membranes at rates inversely proportional to their molecular weights. If the partition coefficients and molecular weights of the compounds are considered simultaneously, it may be possible to estimate which compound will be absorbed more quickly. Absorption half-times of one minute or less have been reported for highly lipid-soluble compounds,[133] whereas for lipid-insoluble compounds (molecular weight 15–200 kDa), half-times of 1 hour have been estimated. The time it takes for peptides

and proteins to peak in the blood system (which depends on the rate of absorption) following lung delivery is molecular-weight-dependent. Small soluble peptides peak 10–30 minutes after administration, while large proteins peak in hours to days.[134]

Most therapeutic agents are weak acids or bases and are present in solution as both the ionized and nonionized species. The nonionized entities are usually lipid-soluble and can diffuse across the cell membrane, whereas ionized molecules are usually unable to penetrate the lipid membrane because of their low lipid solubility. Therefore, the transport through membranes for a weak electrolyte is determined by its pK_a (ie, the negative logarithm of its dissociation constant) and the pH gradient across the membrane. Since the membrane is more permeable to the nonionized form of any drug, it would be expected that weak acids would be absorbed more rapidly at low pH values, while weak bases would be absorbed more quickly at higher pH. The pH of the alveolar epithelial fluid is normally about 6.9.[135] Thus, the extent and rate of pulmonary absorption of weak bases may be more pronounced than that for weak acids. In studies of labeled $^{14}CO_2$ and $H^{14}CO_3^-$, the $H^{14}CO_3^-$ diffused across the pulmonary epithelium at a rate at least 600 times slower than that of the $^{14}CO_2$.[136] The loss of certain molecules such as CO_2, alcohols, and acetone from the lungs is limited by the rate of perfusion rather than the permeability of the alveolar-capillary barrier.[136,137] Acidic solutions (pH 3) of insulin have a higher extent of pulmonary absorption than those of pH 7.[138]

The absorption rate following intratracheal administration of various compounds has been calculated in several animals species.[139] Lipid-insoluble drugs were absorbed approximately 5 times faster in mice than in rats, and roughly 2.5 times more slowly in rabbits than in rats. Lipophilic drugs were absorbed at similar rates in all the tested species.

The effect of osmotic pressure on cell membrane integrity and pulmonary absorption has been studied in detail. Water without solutes was extracted from the tissues when hypertonic solutions were injected into the pulmonary arterial inflow.[140] The water that was removed from the air spaces was essentially devoid of solutes when isolated lungs were filled with isotonic solutions and perfused with hypertonic solutions.[141] This indicates that hydrophilic solutes were not dragged along with the water. The osmolarity of inhaled aerosols could have a variety of effects on the absorption of solutes contained in the inhaled droplets. Hypotonic droplets would be expected to lose water to the relatively hypertonic bronchial walls and therefore shrink before reaching the alveolar surfaces. On the other hand, hypertonic droplets would tend to swell,[130] altering the size of the droplet and therefore, the pattern of deposition along the airways. The administration of a hypotonic solution of insulin to the lungs of rats resulted in increased permeability of this compound, probably because of damage of the integrity of the alveolar membrane.[142]

The relationship between dissolution, drug release rate, and absorption rate, and their effect on the extent of undesired and desired systemic effects has been demonstrated by the pulmonary delivery of slow-release preparations. A drug with a rapid release rate dissolves quickly after pulmonary deposition and is absorbed into the circulation at a rate determined by its chemical structure, as mentioned earlier. Pulmonary administration of a drug incorporated in a slow-release preparation, such as a liposome[143] or microsphere,[144] results in lower pulmonary absorption rate than that of free drug. The rate of absorption of sodium cromoglycate was slower when inhaled as a liposome preparation (dissociation constant [K_a] = 0.027/h) than when inhaled as free drug (K_a = 0.43/h).[145] Triamcinolone acetonide phosphate encapsulated in liposomes is absorbed more slowly (K_a = 0.5/h) than the free drug following intratracheal instillation in rats (K_a = 2/h).[143]

The physicochemical properties of a drug formulation, such as particle size,[21,146] lipophilicity,[22] and crystal form,[21] play a central role in the dissolution rate and, consequently, the absorption rate. Lipophilic drugs with relatively large particle sizes dissolve more slowly than small hydrophilic particles. A drug with a fast dissolution rate dissolves immediately after pulmonary deposition and is absorbed into the systemic circulation at a rate determined by its partition coefficient and molecular weight. A powder formulation of fluticasone propionate, one of the most lipophilic inhaled glucocorticoids, was absorbed more slowly from the airways (mean absorption time = 4.9 h) than less lipophilic glucocorticoids such as flunisolide and budesonide of the same particle sizes (mean absorption time = 0.04 h and 0.2 h, respectively).[147] Formulations with slow dissolution rates may be more appropriate for the local activity of drugs, since the biological activity is directly related to drug concentration at the site of action. However, slowing down the release of inhaled drugs for systemic therapy may be very detrimental, especially for biomolecules.

Drug-Drug Interactions

Multiple drug therapy may be essential in the treatment of several diseases, such as heart failure, cancer, and asthma, and infectious diseases such as tuberculosis and human immunodeficiency virus. The term "drug-drug interaction" refers to the possibility that one drug may alter the intensity of pharmacologic effect of another drug given concurrently. These interactions may be pharmacokinetic, pharmacodynamic (eg, interaction between agonist and antagonist at the level of the receptors), and/or chemical-chemical interactions (Fig. 4).

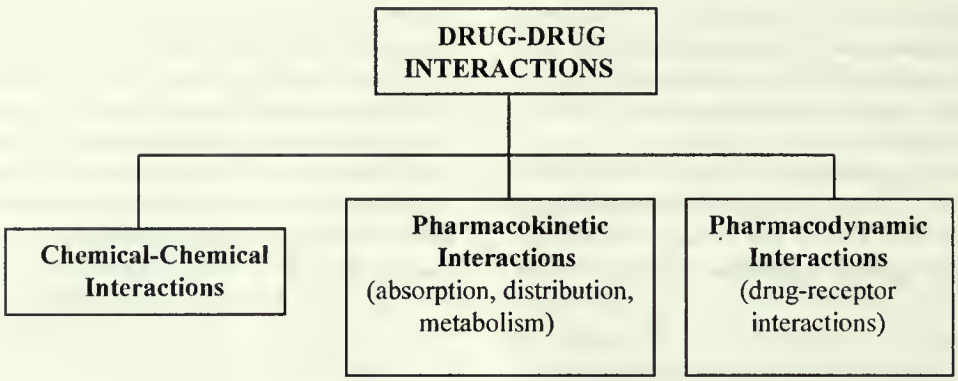

Fig. 4. Schematic representation of drug-drug interactions.

Chemical-Chemical Interactions

Chemical-chemical interactions have mostly been studied in the toxicology of air pollutants, where it was shown that the unwanted effects of certain oxidants may be enhanced in the presence of other aerosols.[148] A study using a guinea pig model found that the irritant effects of SO_2 (the second most abundant air pollutant) are greatly enhanced in the presence of aqueous aerosols of various water-soluble salts.[149] Physical and chemical interactions of aerosolized drugs with the surface active layers and the mucus layer in the respiratory tract are important determinants of the stability and activity of inhaled therapeutic agents.[150] Particulate matter depositing on the alveolar surface can be coated with surfactant and is shown to form liposomes,[151] which may enhance the uptake by macrophages.

Pharmacokinetic Interactions

Although pharmacokinetic interactions can lead to changes in absorption, protein binding, and urinary excretion, the effect on metabolism is generally more pronounced. Drug interactions based on metabolism are mainly associated with phase I metabolism through the cytochrome P-450 system. Thus, if the affected pathway represents the major route of elimination of the drug under consideration, increased or decreased drug plasma/tissue level may prolong or decrease the pharmacologic effect.

The handling of some endogenous and exogenous substances by the pulmonary endothelium involves several processes: uptake and biotransformation (serotonin, prostaglandin E and F), metabolism at the endothelium surface without uptake (angiotensin, adenine nucleotides, bradykinin), and uptake with gradual release unchanged (propranolol, lidocaine, imipramine). The detoxification of serum vasoconstrictor substance (5-HT) on passage through the heart-lung preparation provides the first demonstration of the metabolic function in the lung.[152] The lung selectively removes endogenous norepinephrine, 5-HT, and β-phenylethylamine from the blood[153] and converts angiotensin I to angiotensin II. This implies that drugs with properties similar to these endogenous compounds may also be candidates for metabolism and sequestration by the lung. Treatment of the lung with selective inhibitors of mitochondrial monoamine oxidase markedly reduces the uptake of β-phenylethylamine.[154] Thus, the lung uptake of exogenous compounds similar to β-phenylethylamine may also be reduced by monoamine oxidase inhibitors.

Pre-exposure to one concentration of oxygen mitigates later exposure to 100% oxygen by modifying cellular and enzymatic composition of the lungs.[148] Damage of the alveolar zone by the antioxidant butylated hydroxytoluene can be enhanced by subsequent exposure to oxygen concentration that otherwise would have little if any demonstrable effect. This synergistic interaction between butylated hydroxytoluene and oxygen may result in pulmonary fibrosis.

Inhaled glucocorticoids, the first line of drugs for treating asthma, are metabolized mainly by the liver cytochrome P-450 IIIA enzyme family. These enzymes are both inducible and inhibitive (Table 2). Phenytoin, phenobarbital, rifampicin, promidone, ephedrine, phenylbutazone, and tyrosine are examples of compounds that alter glucocorticoid disposition by inducing liver metabolic capacity.[155]

Table 2. Selected Inhibitors and Inducers of Cytochrome P-450 IIIA

Inhibitors of P-450 IIIA	Inducers of P-450 IIIA
17α-Estradiol	Dexamethasone
17α-Ethynylestradiol	Rifampicin
Testosterone	Phenobarbital
Cyclosporine	Phenytoin
Terfenadine	
Ketokonazole	
Troleandomycin	
Cimetidine	
Erythromycin	

Esterases are present in high levels in alveolar macrophages and, to a lesser extent, in type I and type II alveolar cells.[156] Beclomethasone dipropionate, an inhaled glucocorticoid used for treating asthma, is converted to a more potent compound, beclomethasone monopropionate, by lung esterases.[157] Thus, the coadministration of drugs that are metabolized by esterases with this drug may alter its pharmacologic effect.

Pharmacodynamic Interactions

Pharmacodynamic interactions may occur at a common receptor site or at different sites in an organ, resulting in an addition or inhibitory effect. There is strong evidence to suggest a dynamic interaction between glucocorticoids and β agonists, two classes of drugs used in the treatment of asthma.[158] Glucocorticoids increase the expression of β adrenoreceptors, probably by increasing gene transcription.[159] In addition, β agonists reduce the binding of glucocorticoid receptor to glucocorticoid-response elements within the nucleus by activating a transcription factor that interacts with the glucocorticoid receptor.[160] Interactions at the receptor site have been also found in isolated perfused lung experiments.

Summary

The widespread use of aerosol therapy in the treatment of pulmonary diseases is based on optimizing drug properties and aerodynamic behavior of airborne particulates. In order to understand drug properties and aerodynamic behavior, it is important to recognize that each category of inhaler delivers a product with different physicochemical characteristics, and that these properties determine the site of deposition and the mechanism of clearance from the lungs. The complex interplay of these properties and the physiology and anatomy of the lungs must be considered to fully understand the implications for drug delivery. The aerodynamic behavior of aerosols under various inspiratory flow conditions influences the site of deposition. Once the particle comes to rest in the lungs, mechanisms of clearance are invoked, including dissolution and absorption, or, for more insoluble materials, mucociliary transport or cell-mediated transport. Finally the pharmacokinetics of drug disposition dictate the pharmacodynamic effects of the drugs responsible for efficacy.

REFERENCES

1. Neville A, Palmer JB, Gaddie J, May CS, Palmer KN, Murchison LE. Metabolic effects of salbutamol: comparison of aerosol and intravenous administration. Br Med J 1977;1(6058):413–414.
2. Newman S, Clarke S. Aerosols in medicine: principles, diagnosis and therapy. In: Moren F, Newhouse M, Dolovich, M, editors. Aerosol in therapy. Amsterdam: Elsevier; 1985.
3. Clark TJ. Effect of beclomethasone dipropionate delivered by aerosol in patients with asthma. Lancet 1972;1(7765):1361–1364.
4. Clarke SW, Newman SP. Therapeutic aerosols. 2. Drugs available by the inhaled route. Thorax 1984;39(1):1–7.
5. Lourenco R, Cotromanes E. Clinical aerosols II. Therapeutic aerosols. Arch Int Med 1982;142(13):2299–2308.
6. Byron PR, Patton JS. Drug delivery via the respiratory tract. J Aerosol Med 1994;7(1):49–75.
7. Patton J, Platz R. Routes of delivery: case studies pulmonary delivery of peptides and proteins for systemic action. Adv Drug Deliv Rev 1992;8:179–196.
8. Hickey AJ, Martonen TB. Behavior of hygroscopic pharmaceutical aerosols and the influence of hydrophobic additives. Pharm Res 1993;10(1):1–7.
9. Schlesinger RB. Comparative deposition of inhaled aerosols in experimental animals and humans: a review. J Toxicol Environ Health 1985;15(2):197–214.
10. Atkins P, Clark AR. Drug delivery to the respiratory tract and drug dosimetry. J Aerosol Med 1994;7(1):33–38.
11. Lippmann M, Schlesinger RB. Interspecies comparisons of particle deposition and mucociliary clearance in tracheobronchial airways. J Toxicol Environ Health 1984;13(2–3):441–469.
12. Byron PR. Prediction of drug residence times in regions of the human respiratory tract following aerosol inhalation. J Pharm Sci 1986; 75(5):433–438.
13. Anderson M, Philipson K, Svartengren M, Camner P. Human deposition and clearance of 6-um particles inhaled with an extremely low flow rate. Exp Lung Res 1995;21(1):187–195.
14. Stahlhofen W, Rudolf G, James A. Intercomparison of experimental regional aerosol deposition data. J Aerosol Med 1989;2:285–308.
15. Svartengren K, Philipson K, Svartengren M, Anderson M, Camner P. Tracheobronchial deposition and clearance in small airways in asthmatic subjects. Eur Respir J 1996;9(6):1123–1129.
16. Barnes PJ, Basbaum CB, Nadel JA. Autoradiographic localization of autonomic receptors in airway smooth muscle: marked differences between large and small airways. Am Rev Respir Dis 1983;127(6): 758–762.
17. Brown RA Jr, Schanker LS. Absorption of aerosolized drugs from the rat lung. Drug Metab Dispos 1983;11(4):355–360.
18. Effros RM, Mason GR. Measurements of pulmonary epithelial permeability in vivo. Am Rev Respir Dis 1983;127(5 Pt 2):S59–S65.
19. Enna S, Schanker LS. Absorption of saccharides and urea from the rat lung. Am J Physiol 1972;222(2):409–414.
20. Burton JA, Schanker LS. Absorption of antibiotics from the rat lung. Proc Soc Exp Biol Med 1974;145(3):752–756.
21. Byron P, Phillips E. Absorption, clearance and dissolution on the lung respiratory drug delivery. Boca Raton FL: CRC; 1990: 107–141.
22. Johnson, M. Pharmacodynamics and pharmacokinetics of inhaled glucocorticoids. Allergy Clin Immunol 1996;97(1 Pt 2):169–177.
23. Gonda I. Drugs administered directly into the respiratory tract: modeling of the duration of effective drug levels. J Pharm Sci 1988; 77(4):340–346.
24. Suarez S, Gonzalez-Rothi RJ, Schreier H, Hochhaus G. Effect of dose and release rate on pulmonary targeting of liposomal triamcinolone acetonide phosphate. Pharm Res 1998;15(3):461–465.
25. Dolovich M. Lung dose, distribution, and clinical response to therapeutic aerosols. Aerosol Sci Tech 1993;18:230–240.
26. Schultz R, Miller N, Christensen J. Method for evaluation of suspension characteristics relevant to metered dose inhaler formulations. Pharm Res 1990;7:s-88.
27. Konig P. Spacer devices used with metered-dose inhalers: breakthrough or gimmick? Chest 1985;88(2):276–284.

28. Sciarea JJ, Cutie A. Simulated respiratory system for in vitro evaluation of two inhalation delivery systems using selected steroids. J Pharm Sci 1978;67(10):1428–1431.
29. Dolovich J. New delivery systems and propellants. Can Respir J 1999;6(3):290–295.
30. Hickey A. Inhalation therapy. Drug Topics 1989;133:60–69.
31. Gonda I.Therapeutic aerosols. In: Aulton M, editor. Pharmaceutics: the science of dosage form design. Edingburgh: Churchill Livingstone; 1988: 341.
32. Epstein SW, Manning CP, Ashley MJ, Corey PN. Survey of the clinical use of pressurized aerosol inhalers. Can Med Assoc J 1979; 120(7):813–816.
33. Dolovich M, Ruffin RE, Roberts R, Newhouse MT. Optimal delivery of aerosols from metered dose inhalers. Chest 1981;80(6 Suppl): 911–915.
34. Gupta P, Hickey A. Contemporary approaches in aerosolized drug delivery to the lung. J Control Rel 1991;17:129–148.
35. Dolovich M. Rationale for spacer use in children. Pediatr Pulmonol Suppl 1997;16:184–185.
36. Newman SP, Moren F, Pavia D, Little F, Clarke SW. Deposition of pressurized suspension aerosols inhaled through extension devices. Am Rev Respir Dis 1981;124(3):317–320.
37. Byron P, R Jashnani, Germin S. Efficiency of aerosolization from dry powder blends of terbutaline sulphate and lactose NF with different particle size distribution. Pharm Res 1990;7:81s.
38. Malem H, Ward M, Henry D, Smith WH, Gonda I. Early experience with a vertical spinning disc nebuliser. Lancet 1981;2(8248):644–646.
39. Brown K. The formulation and evaluation of powders for inhalation. In: Ganderton D, Jones, T, editors. Drug delivery to the respiratory tract. England: VCH and Ellis Horwood Ltd; 1987: 119–123.
40. Ferron G. The size of soluble aerosol particles as a function of the humidity of the air. Application to the human respiratory tract. J Aerosol Sci 1977;8:251–267.
41. Mercer T. Properties of aerosols. In: Mercer T, editor. Aerosol technology in hazard evaluation. New York: Academic Press; 1973.
42. Phipps P, Borham P, Gonda I, Bailey D, Bautovich G, Anderson S. A rapid method for evaluation of diagnostic radioaerosol delivery systems. Eur J Nucl Med 1987;13(4):183–186.
43. Lewis R. Therapeutic aerosols. In: Cumming G, Bonsignore G, editors. Drugs and the lungs, Vol 63. New York: Plenum Press; 1984.
44. Schlesinger RB. Clearance from the respiratory tract. Fundam Appl Toxicol 1985;5(3):435–450.
45. Anderson PJ, Wilson JD, Hiller FC. Respiratory tract deposition of ultrafine particles in subjects with obstructive or restrictive lung disease. Chest 1990;97(5):1115–1120.
46. Carpenter RL. Aerosol deposition modeling using ACSL. Drug Chem Tox 1999;22(1):73–90.
47. O'Doherty MJ, Miller RF. Aerosols for therapy and diagnosis. Eur J Nucl Med 1993;20(12):1201–1213.
48. Yu J, Chien YW. Pulmonary drug delivery: physiologic and mechanistic aspects. Crit Rev Ther Drug Carrier Syst 1997;14(4):395–453.
49. Brain JD, Valberg PA. Deposition of aerosols in the respiratory tract (review). Am Rev Respir Dis 1979;120(6):1325–1373.
50. Lippmann M. Regional deposition of particles in the human respiratory tract handbook of physiology. American Physioligical Society; 1977.
51. Zainudin BM. Therapeutic aerosol: principles and practices. Med J Malaysia 1993;48(3):259–268.
52. Byron P. Some future perspectives for unit dose inhalation aerosols. Drug Dev Ind Pharm 1976;12:993–1015.
53. Byron P. Pulmonary targeting with aerosols. Pharm Tech 1987;11: 42–56.
54. Bailey M, Kreyling W, Andre S, Batchelor A, Collier C, Drosselmeyer E, et al. An interspecies comparison of the lung clearance of inhaled mododisperse cobalt oxide particles. Part I: objectives and summary of results. J Aerosol Sci 1989;20:169–188.
55. Cuddihy R. Respiratory tract retention of inhaled particles in experimental animals. Inhalation Toxicology Research Institute Annual Report 1976;137–142.
56. Cuddihy R. Mathematical models for predicting clearance of inhaled radioactive substances. Lung Model Inhal Radioactive Mater 1984; 167–179.
57. Hakkinen AM, Uusi-Heikkila H, Jarvinen M, Saali K, Karhumaki L. The effect of breathing frequency on deposition of drug aerosol using an inhalation-synchronized dosimeter in healthy adults. Clin Physiol 1999;19(3):269–274.
58. Gonda I. Aerosols for delivery of therapeutic and diagnostic agents to the respiratory tract. Crit Rev Ther Drug Carrier Syst 1990;6(4): 273–313.
59. Valberg PA, Brain JD, Sneddon SL, Le Mott SR. Breathing patterns influence aerosol deposition sites in excised dog lungs. J Appl Physiol 1982;53(4):824–837.
60. Mygind N. Structure and function of the respiratory tract. In: Moren F, Newhouse M, editors. Aerosols in medicine. New York: Elsevier; 1985.
61. Wiebel E. The lung: scientific foundations. New York: Raven Press; 1991.
62. Mercer RR, Russell ML, Roggli VL, Crapo JD. Cell number and distribution in human and rat airways. Am J Respir Cell Mol Biol 1994;10(6):613–624.
63. Weibel E. Morphometrics of the lung. Handbook of physiology, Vol 1. Washington DC: American Physiological Society; 1964: 285.
64. Batenburg JJ. Surfactant phospholipids: synthesis and storage. Am J Physiol 1992;262(4 Pt 1):L367–L385.
65. Hawgood S. Pulmonary surfactant apoproteins: a review of protein and genomic structure. Am J Physiol 1989;257(2 Pt 1):L13–L22.
66. Miyamura K, Malhotra R, Hoppe HJ, Reid K, Phizackerley P, Macpherson P, Lopez-Bernal A. Surfactant proteins A (SP-A) and D (SP-D): levels in human amniotic fluid and localization in the fetal membranes. Biochim Biophys Acta 1994;1210(3):303–303.
67. van Iwaarden F, Welmers B, Verhoef J, Haagsman HP, van Golde LM. Pulmonary surfactant protein A enhances the host-defense mechanism of rat alveolar macrophages. Am J Respir Cell Mol Biol 1990;2(1):91–98.
68. Evander E, Wollmer P, Jonson B, Lachmann B. Pulmonary clearance of inhaled 99mTc-DTPA: effects of surfactant depletion by lung lavage. J Appl Physiol 1987;62(4):1611–1614.
69. Wollmer P, Evander E, Jonson B. Pulmonary clearance of inhaled 99m Tc-DTPA: effect of surfactant depletion in rabbits. Clin Physiol 1986;6(1):85–89.
70. Sanderson MJ, Sleigh MA. Ciliary activity of cultured rabbit tracheal epithelium: beat pattern and metachrony. J Cell Sci 1981;47:331–347.
71. Lucas A, Douglas L. Principles underlying ciliary activity in the respiratory tract. Arch Otolaryngol 1934;34:495.
72. Jeffrey PK. The origins of secretions in the lower respiratory trac. Eur J Respir Dis Suppl 1987;153:34–42.
73. Rogers DF, Dewar A. Neutral control of airway mucus secretion. Biomed Pharmacother 1990;44(9):447–453.
74. Richardson PS, Peatfield AC. The control of airway mucus secretion. Eur J Respir Dis Suppl 1987;153:43–51.
75. Sturgess J, Reid L. An organ culture study of the effect of drugs on the secretory activity of the human bronchial submucosal gland. Clin Sci 1972;43(4):533–543.

76. Svartengren K, Ericsson CH, Svartengren M, Mossberg B, Philipson K, Camner P. Deposition and clearance in large and small airways in chronic bronchitis. Exp Lung Res 1996;22(5):555–576.
77. Scherer PW. Mucus transport by cough. Chest 1981;80(6 Suppl): 830–833.
78. Oberdorster G. Lung clearance of inhaled insoluble and soluble particles. J Aerosol Med 1988;1:289–330.
79. Devereux TR, Domin BA, Philpot RM. Xenobiotic metabolism by isolated pulmonary cells. Pharmacol Ther 1989;41(1–2):243–256.
80. Bend JR, Serabjit-Singh CJ, Philpot RM. The pulmonary uptake, accumulation and metabolism of xenobiotics. Annu Rev Pharmacol Toxicol 1985;25:97–125.
81. Foster WM, Langenback E, Bergofsky E. Measurement of tracheal and bronchial mucus velocities in man: relation to lung clearance. J Appl Physiol 1980;48(6):965–971.
82. Kimoto A, Saitou M, Hirano Y, Iwai T, Tomioka K, Miyata K, Yamada T. A new, simple method for measuring mucociliary clearance in guinea pigs. Pulm Pharmacol Thera 1999;12(1):49–54.
83. Patrick G, Stirling C. Measurement of mucociliary clearance from the trachea of conscious and anesthetized rats. J Appl Physiol 1977; 42(3):451–455.
84. Svartengren M, Widtskiold-Olsson K, Philipson K, Camner P. Retention of particles on the first bifurcation and the trachea of rabbits. Bull Physiopathol Respir 1981;17(1):87–91.
85. Bailey MR, Fry FA, James AC. The long-term clearance kinetics of insoluble particles from the human lung. Ann Occup Hyg 1992; 26(1–4):273–290.
86. Falk R, Philipson K, Svartengren M, Jarvis N, Bailey M, Camner P. Clearance of particles from small ciliated airways. Exp Lung Res 1997;23(6):495–515.
87. Lafortuna CL, Fazio F. Acute effect of inhaled salbutamol on mucociliary clearance in health and chronic bronchitis. Respiration 1984;45(2):111–123.
88. Fazio F, Lafortuna CL. Beclomethasone dipropionate does not affect mucociliary clearance in patients with chronic obstructive lung disease. Respiration 1986;50(1):62–65.
89. Foster WM, Langenback EG, Bergofsky EH. Disassociation in the mucociliary function of central an peripheral airways of asymptomatic smokers. Am Rev Respir Dis 1985;132(3):633–639.
90. Messina MS, O'Riordan TG, Smaldone GC. Changes in mucociliary clearance during acute exacerbations of asthma. Am Rev Respir Dis 1991;143(5 Pt 1):993–997.
91. Svartengren M, Ericsson CH, Philpson K, Mossberg B, Camner P. Tracheobronchial clearance in asthma-discordant monozygotic twins. Respiration 1989;56(1–2):70–79.
92. Brain JD. Mechanisms, measurement, and significance of lung macrophage function. Environ Health Perspect 1992;97:5–10.
93. Stone KC, Mercer RR, Gehr P, Stockstill B, Crapo JD. Allometric relationships of cell numbers and size in the mammalian lung. Am J Respir Cell Mol Biol 1992;6(2):235–243.
94. Gehr P, Geiser M, Im Hof V, Schurch S, Waber U, Baumann M. Surfactant and inhaled particles in the conducting airways: structural, stereological, and biophysical aspects. Microsc Res Technol 1993;26(6):423–436.
95. Beck BD, Brain JD, Bohannon DE. An in vivo hamster bioassay to assess the toxicity of particulates for the lungs. Toxicol Appl Pharmacol 1982;66(1):9–29.
96. Lalor C, Atkins K, Concessio N, Pettis R, Hickey A. Lung deposition and alveolar macrophage uptake of microparticles from suspension aerosols in guinea pigs. Society of Toxicology, 35th Annual Meeting, Anaheim, CA; 1996.
97. Oberdorster G, Ferin J, Gelein R, Soderholm SC, Finkelstein J. Role of the alveolar macrophage in lung injury: studies with ultrafine particles. Environ Health Perspect 1992;97:193–199.
98. Snipes MB, Clem MF. Retention of microspheres in the rat lung after intratracheal instillation. Environ Res 1981;24(1):33–41.
99. Oberdorster G, Cox C, Gelein R. Intratracheal instillation versus intratracheal inhalation of tracer particles for measuring lung clearance function. Exp Lung Res 1997;23(1):17–34.
100. Ferin J. Pulmonary retention and clearance of particles. Toxicol Lett 1994;72(1–3):121–125.
101. Green GM, Jakab GJ, Low RB, Davids GS. Defense mechanisms of the respiratory membrane. Am Rev Respir Dis 1977;115(3):479–514.
102. Kreyling W, Ferron G, Schumann G, Heilmann P. Macrophage mediated particle transport form the lungs. J Aerosol Med 1990;3: 285.
103. Snipes MB, Boeker BB, McClellan RO. Retention of monodisperse onpolydisperse aluminosilicate particles inhaled by dogs, rats and mice. Toxicol Appl Pharmacol 1983;69(3):345–362.
104. Bowden DH. Macrophages, dust, and pulmonary diseases. Exp Lung Res 1987;12(2):89–107.
105. Snipes MB, Chavez GT, Muggenberg BA. Disposition of 3-,7- and 13-microns microspheres instilled into lungs of dogs. Environ Res 1984;33(2):333–342.
106. Ferin J, Oberdorster G, Penney DP. Pulmonary retention of ultrafine and fine particles in rats. Am J Respir Cell Mol Biol 1992; 6(5):535–542.
107. Ferin J, Oberdorster G, Sebring R, Lehnert B. Are particles cleared from the pulmonary interstitium via the airways? J Aerosol Med 1992;5:286.
108. Shepherd VL. The role of the respiratory burst of phagocytes in host defense. Semin Respir Infect 1986;1(2):99–106.
109. Sugar AM, Field KG. Characterization of murine bronchoalveolar macrophage respiratory burst: comparison of soluble and particulate stimuli. J Leuko Biol 1988;44(6):500–507.
110. Patton J. Mechanisms of macromolecule absorption by the lungs. Adv Drug Del Rev 1996;19:3–36.
111. Olver RE, Schneeberger EE, Walters DV. Epithelial solute permeability, ion transport and tight junction morphology in the developing lung of the fetal lamb. J Physiol (Lond) 1981;315:395–412.
112. Schanker LS. Drug absorption from the lung. Biochem Pharmacol 1978;27(4):381–385.
113. Gardiner T, Schanker L. Absorption of disodium cromoglycate form the rat lung: evidence of carrier transport. Xenobiotica 1974;4:725–731.
114. Goodman BE, Wangensteen D. Alveolar epithelium permeability to small solutes: developmental changes. J Appl Physiol 1982;52(1): 3–8.
115. Kim K, Matsukama Y, Lee V, Crandall E. Characteristics of albumin absorption across rat alveolar epithelial cell monolayers (abstract). FASEB J 1995;9:A569.
116. Kim KJ, Crandall ED. Heteropore populations of bullfrog alveolar epithelium. J Appl Physiol 1983;54(1):140–146.
117. Chandra T, Miller IF, Yeates DB. A pore transport model for pulmonary alveolar epithelium. Ann Biomed Eng 1992;20(4):481–494.
118. Mostov KE, Simister NE. Transcytosis. Science 1985;43(2 Pt 1): 389–390.
119. Gil J. Number and distribution of plasmalemmal vesicles in the lung. Fed Proc 1983;42(9):2414–2418.
120. Gonzales-Crussi FW, Boston R. The absorptive function of the neonatal lung: ultrastructural study of horseradish peroxidase uptake at the onset of ventilation. Lab Invest 1972;26(1):114–121.
121. Kim K, Rattan V, Oh P, Schnitzer J, Kalra V, Crandall E. Specific albumin-binding protein in alveolar epithelial cel monolayers (abstract). Am J Respir Crit Care Med 1995;151(4 Pt 2):A190.

122. Schnitzer J, Oh P. Albondin-mediated capillary permeability to albumin: differential role of receptors in endothelial transcytosis and endocytosis of native and modified albumins. J Biol Chem 1994;269:A6072–A6082.
123. Lisanti MP, Scherer PE, Vidugiriene J, Tang Z, Hermanowski-Vosatka A, Tu YH, et al. Characterization of caveolin-rich membrane domains isolated from an endothelial-rich source: implications for human disease. J Cell Biol 1994;126(1):111–126.
124. Smith P, Yeulet S, Citerone D, Drake F, Cook M, Wall D, Marcello J. SK&F 110679: comparison of absorption following oral or respiratory administration. J Control Rel 1994;28:67–77.
125. Bartels H, Oestern HJ, Voss-Wermbter G. Communicating-occluding junction complexes in the alveolar epithelium: a freeze-fracture study. Am Rev Respir Dis 1980;121(6):1017–1024.
126. Schneegerger EE. Structure of intercellular junctions in different segments of the intrapulmonary vasculature. Ann NY Acad Sci 1982;54:63.
127. Reed CJ, Lock EA, DeMatteis F. NADPH: cytochrome P-450 reductase in olfactory epithelium: relevance to cytochrome P-450-dependent reactions. Biochem J 1986;240(2):585–592.
128. Bundgaard M. The three-dimensional organization of tight junctions in a capillary endothelium revealed by serial-section electron microscopy. J Ultrastruct Res 1984;88(1):1–17.
129. Schneeberger E, Karnovsky M. Substructure of intercellular junctions in freeze-fractured alveolar-capillary membranes of mouse lung. Circ Res 1976;38(5):405–411.
130. Effros RM. Solute transport following aerosol deposition in the lungs. In: Hickey J, editor. Inhalation aerosols: physical and biological basis for therapy. Vol 94. New York: Marcel Dekker; 1996: 139–154.
131. Normand IC, Oliver RE, Reynolds ED, Strang LB. Permeability of lung capillaries and alveoli to non-electrolytes in the foetal lamb. J Physiol (Lond) 1971;219(2):303–330.
132. Enna SJ, Schanker LS. Absorption of drugs from the rat lung. Am J Physiol 1972;223(5):1227–1231.
133. Lanman RC, Gillilan RM, Schanker LS. Absorption of cardiac glycosides from the rat respiratory tract. J Pharmacol Exp Ther 1973;187(1):105–111.
134. Adjei L, Gupta P. Inhalation delivery of therapeutic peptides and proteins. In: Lenfant C, editor. Lung biology in health and disease. Vol 107. New York: Marcel Dekker; 1997: 1–913.
135. Nielson DW, Goerke J, Clements JA. Alveolar subphase pH in the lungs of anesthetized rabbits. Proc Natl Acad Sci USA 1981;78(11): 7119–7123.
136. Effros RM., Mason G, Silverman P. Role of perfusion and diffusion in 14CO2 exchange in the rabbit lung. J Appl Physiol 1981;51(5): 1136–1144.
137. Effros RM., Mason GR, Reid E, Graham L, Silverman P. Diffusion of labeled water and lipophylic solutes in the lung. Microvasc Res 1985;29(1):45–55.
138. Okumura K, Iwakawa S, Yoshida T, Seki T, Komada F. Intratracheal delivery of insulin: absorption from solution and aerosol by rat lung. Int J Pharm 1992;88:63–73.
139. Schanker LS, Mitchell EW, Brown RA Jr. Species comparison of drug absorption from the lung after inhalation or intratracheal injection. Drug Metab Dispos 1986;14(1):79–88.
140. Effros RM. Osmotic extraction of hypotonic fluid from the lungs. J Clin Invest 1974;54(4):935–947.
141. Effros R, Mason GR, Sietsema K, Hukkanen J, Silverman P. Pulmonary epithelial sieving of small solutes in rat lungs. J Appl Physiol 1988;65(2):640–648.
142. Yyping L, Mitra A. Effects of formulation variables on the pulmonary delivery of insulin. Drug Dev Ind Pharm 1994;20:2017–2024.
143. Suarez S. Biopharmaceutical aspects relevant to pulmonary targeting of inhaled glucocorticoids: application to liposomes and dry powders. Department of Pharmaceutics, University of Florida, Gainesville; 1997: 72–106.
144. Suarez S, O'Hara P, Hickey A. Uptake and disposition of rhodamine-labeled rifampicin-loaded poly(lactide-co-glycolide) microspheres following powder insufflation. Pharm Res 1998;1:S208.
145. Taylor KM, Taylor G, Kellaway IW, Stevens J. The influence of liposomal encapsulation on sodium cromoglycate pharmacokinetics in man. Pharm Res 1989;6(7):633–636.
146. Fielding RM, Abra RM. Factors affecting the release rate of terbutaline from liposome formulations after intratracheal instillation in the guinea pig. Pharm Res 1992;9(2):220–223.
147. Meibohm B, Hochhaus G, Moellmann H, Barth J, Derendorf H. Absorption profile of inhaled corticosteroids. Pharm Res 1997;14:S141.
148. Witschi HP, Hakkinen PJ. The role of toxicological interactions in lung injury (review). Environ Health Perspect 1984;55:139–148.
149. Amdurm M, Underhill D. The effects of various aerosols on the response of guinea pigs to sulfur dioxide. Arch Envirom Health 1968;16:462–468.
150. Kilburn KH. Particles causing lung disease. Environ Health Perspect 1984;55:97–100.
151. Curti P, Genghini M. Role of surfactant in alveolar defense against inhaled particles. Respiration 1989;1:60.
152. Gaddum J, Hebb C, Silver A, Swan A. 5-Hydroxytryptamine: pharmacological action and destruction in perfused lungs. Q J Exp Physiol 1953;38:255–262.
153. Bakhle YS, Youdim MB. The metabolism of 5-hydroxytryptamine and beta-phenylethylamine in perfused rat lung and in vitro. Br J Pharmacol 1979;65:147–154.
154. Alabaster V. Inactivation of endogenous amines in the lungs. In: Bakhl, Y, Vane J, editors. Metabolic functions of the lung. Vol 3. New York: Marcel Dekker; 1977: 31.
155. Edsbäcker S, Jendbro M. Modes to achieve topical selectivity of inhaled glucocorticosteroids-focus on budesonide. In: Dalby R, Byron P, editors. Respiratory drug delivery VI. Hilton Head SC: Interphar Press; 1998: 71–82.
156. Meban C. Non-specific esterase in the alveolar tissues of hamster lung: an electron microscope study. Acta Anat (Basel) 1980;108(2): 184–192.
157. Andersson P, Ryrfeldt A. Biotransformation of the topical glucocorticoids budesonide and beclomethasone 17 alpha.21-dipriopionate in human liver and lung homogenate. J Pharm Pharmacol 1984;36(11):763–765.
158. Arnaud A, Charpin J. Interaction between corticosteroids and beta$_2$ agonists in acute asthma. Eur J Respir Dis Suppl 1982;122:126–131.
159. Mak JCW, Adcock I, Barnes PJ. Dexamethasone increases beta$_2$-adrenoreceptor gene expression in human lung (abstract). Am Rev Respir Dis 1992;145(4 Pt 2):A834.
160. Peters MJ, Adcock IM, Brown CR, Barnes PJ. Beta agonist inhibition of steroid-receptor DNA binding activity in human lung (abstract). Am Rev Respir Dis 1993;147(4 Pt 2):A772.

Aerosolized Antibiotics: Current and Future

Gerald C Smaldone MD PhD and Lucy B Palmer MD

Introduction
Ambulatory Patients–Cystic Fibrosis
Principles of Aerosol Therapy in the Ambulatory Patient
The Intubated Patient
Measuring Aerosol Delivery in the Intubated Patient
Targeted Aerosol Prophylaxis in the Intubated Patient
Summary
[Respir Care 2000;45(6):667–675] *Key words: aerosol, antibiotic, pulmonary deposition, ventilator-associated pneumonia.*

Introduction

This paper is written for the practicing pulmonologist, critical care intensivist, and respiratory therapist active in the treatment of patients with respiratory infections. At present, aerosolized antibiotic therapy is an unproven therapy. For the average patient, the caregiver does not routinely think of the aerosol route in the treatment of bronchitis or pneumonia. Yet, for the clinical investigator interested in aerosol therapy, aerosolized antibiotics have always been thought of as having important potential for the treatment of respiratory infections. All of the classic advantages of aerosol therapy apply to antibiotics. They treat the target organ directly and spare the body systemic toxicity. However, in spite of the attractiveness of the aerosol route for the treatment of respiratory infection, aerosolized antibiotics have not been recognized as effective, except for a few conditions, such as cystic fibrosis. This paper reviews the history of aerosolized antibiotic therapy and attempts to define modern concepts of clinical aerosol delivery that may allow more definitive studies to define the true potential of this mode of therapy. Because of the differences in day-to-day care, instrumentation of the airway, and risks of infection, we address ambulatory patients and intubated patients separately.

Ambulatory Patients–Cystic Fibrosis

Topical treatment of the respiratory tract via aerosolization or instillation of antibiotics has been practiced anecdotally for years in patients with cystic fibrosis.[1–4] The lack of effective oral therapy for the treatment of Gram-negative infections forced clinicians to develop methods for the off-label use of systemic antibiotics as aerosols. In addition, in patients with tracheostomies, similar preparations were used for direct instillation. Most of the older literature consisted of case reports in which aerosolized antibiotics were used to stabilize a patient's respiratory function. A few large-scale trials were undertaken, primarily in Europe, which indicated that some clinical benefit could be realized.[3] These effects were defined as small but statistically significant increases in respiratory function, as well as reduced frequency of exacerbations requiring hospitalization. These observations were further supported by a single placebo-controlled study that defined the role of aerosolized tobramycin in the United States.[5] As a group, these studies indicate that patients with the typical flora found in cystic fibrosis (Gram-negative organisms) respond to aerosolized therapy with an increase in function, estimated by spirometric improvements of 5–10%. In addition, their decline in pulmonary function appears to be blunted, with an increased interval between hospitalizations requiring parenteral antibiotic therapy.

In one study, instilled tobramycin was used as adjunctive therapy in hospitalized patients in conjunction with parenteral antibiotics, in an attempt to improve clinical response. Clinical outcome was not affected.[6]

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Thus, in cystic fibrosis (thought to be a paradigm for bronchiectasis in general) and possibly bronchitis, aerosolized antibiotic therapy is probably a useful therapy, but it has not displaced systemic therapy as the most important modality for the treatment of respiratory infection. It is not clear why this is so. Systemic agents, especially aminoglycosides, have been criticized as primary agents of lung infection because of limited penetration into respiratory secretions. This is the rationale for aerosolized and other forms of topical therapy to the respiratory tract. In studies where sputum levels have been measured following aerosolized antibiotics, increases in drug concentration are often reported to be an order of magnitude higher than levels expected from parenteral regimens. Despite these differences, clinical experience indicates that systemic therapy is more effective than aerosolized therapy in these patients. If levels of antibiotics, as measured in secretions, was the dominant factor responsible for the success of therapy, aerosolized antibiotics should displace systemic therapy as the primary mode of treatment, especially in hospitalized patients. These observations would suggest that the issue of antibiotic penetration into the inflamed, infected airway and secretions is not completely understood and that the sputum level, especially for aminoglycosides, may not adequately describe the pharmacokinetics of these drugs to the point where we can predict their effectiveness from levels alone.

From a practical point of view, the day-to-day use of aerosolized antibiotic therapy has been confined to off-label use in cystic fibrosis and, now, with approved tobramycin, routine therapy in patients with well established disease. Patients who do not have cystic fibrosis but do have advanced bronchiectasis often behave similarly to cystic fibrosis patients in that their respiratory tracts become colonized with Gram-negative organisms such as Pseudomonas. In the past, it would not have been unusual for pulmonologists to treat these patients in a similar manner to patients with cystic fibrosis—that is, with aerosolized off-label use of aminoglycosides. In more recent years, however, the advent of useful oral agents for the suppression of Gram-negative infection has become the first line of therapy. Thus, in all forms of severe bronchiectasis, aerosolized therapy remains adjunctive at best.

Antibiotics serve as a useful paradigm for modern aerosolized drugs. Most aerosolized agents, especially those delivered via nebulizer, are bronchodilators used to treat asthma patients. Aerosolized bronchodilators can be titrated directly to the patient's symptoms. Response to therapy can be assessed in real time using spirometry and other indices of respiratory distress as end points. Bronchodilators, which are safe enough to deliver to the patient continuously, allow individual titration of dose to the measured response at the bedside. This approach is not possible with aerosolized antibiotics. The dose-response relationship can only be estimated, and our understanding of the mechanisms of therapy appears to be incomplete. An approach to defining the important variables in these patients is described below.

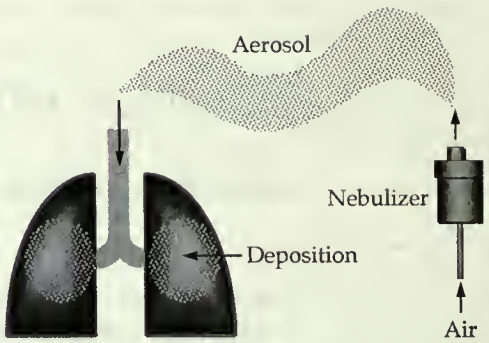

Fig. 1. Components of an aerosol delivery system: the aerosol, the aerosol generator (nebulizer shown), and the patient's respiratory tract.

Principles of Aerosol Therapy in the Ambulatory Patient

There are three components to an aerosol delivery system (Figure 1): (1) the aerosol, which is characterized by the mass median aerodynamic diameter (MMAD), (2) the aerosol generator, in this case a nebulizer, and (3) the pathophysiologic condition of the patient's lung. All three factors must be considered in the delivery of an aerosolized drug. Several reviews have addressed these principles in detail.[7–9] Briefly, the deposition of an aerosolized drug can be quantitated by measuring the variables defined in Equation 1 (the mass balance):

$$\text{deposition} = \text{inhaled mass} - \text{exhaled mass}$$

The *inhaled mass* is an important term, which is defined by the aerosol delivery system as well as by the patient's breathing pattern.[10] Many aerosolized antibiotics are delivered via nebulization. It has been generally observed that the efficiency of a nebulizer depends on the nebulizer itself, the physical properties of the solution, and the pattern of breathing. All of these factors are summed in the *inhaled mass*, and this quantity can be studied in vitro in bench experiments (Fig. 2). As shown in Figure 2, in vitro testing can also facilitate measurement of the aerodynamic characteristics of the aerosol (MMAD), often by using cascade impaction. Prior to clinical studies, bench testing is useful to confirm the preservation of the chemical structure of the drug after nebulization, the aerodynamic behavior of the particles, adequate efficiency of the nebulizer, and, for gamma camera studies, to define the relationship between radiolabel and drug activity. For a given patient, the individual quantities describing deposi-

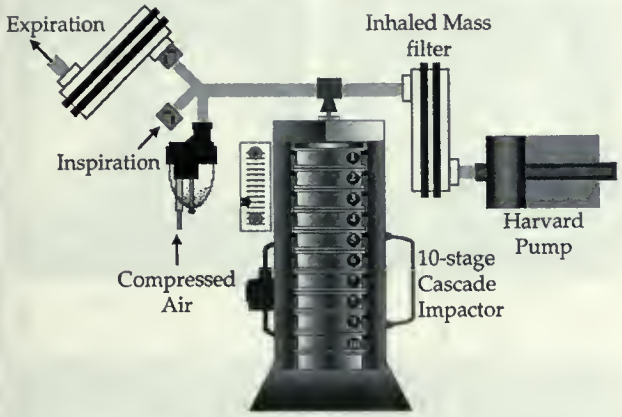

Fig. 2. Components of a standard bench setup for characterizing aerosol delivery systems. The piston pump simulates a given breathing pattern. The aerosol generator (nebulizer) is configured with tubing and connectors appropriate for the clinical situation. Filters are interposed to capture particles that would be inhaled by the patient (inhaled mass filter). Particles not presented to the patient are captured by the filter on the exhalation line. A cascade impactor is used to measure mass median aerodynamic diameter.

tion as defined by Equation 1 can be directly measured during aerosol delivery, using absolute filters or gamma camera techniques, as illustrated in Figure 3. Equation 1 determines the total dose of drug to the patient. Regional studies employing radioisotopes and the gamma camera define the quantity of deposited aerosol that actually resides in the lung and its distribution within the airways.

The first study measuring these variables in patients with cystic fibrosis was performed by Ilowite et al in 1987.[11] They used the mass balance filter technique to measure deposition in a group of ambulatory patients with cystic fibrosis who were inhaling aerosolized gentamicin nebulized during spontaneous breathing. The initial quantity of drug placed in the nebulizer was 160 mg and the device produced an aerosol with an MMAD of 1.1 μm. Figure 4 illustrates the importance of breathing pattern. With the patients breathing tidally in a steady state but without further guidance from the investigators (non-controlled pattern), the quantity of drug deposited in the lungs varied by an order of magnitude. This variation was significantly reduced in some of those patients by repeating the deposition measurement with a standardized controlled breathing pattern. Following a single treatment, the deposition of drug in the lungs was related to levels in expectorated sputum (Figure 5). Gentamicin levels ranged from 50 μg/mL to 800 μg/mL of expectorated sputum. The level of antibiotic decreased rapidly, as measured by serial samples of expectorated sputum.

While the levels of antibiotic in the sputum seemed to vary in a random manner, these authors found that sputum levels could be predicted using a combination of data from the mass balance measurement and regional analysis from the gamma camera. As illustrated in Figure 6, peak sputum level was not clearly related to lung deposition. However, the pattern of deposited aerosol within the lung could be

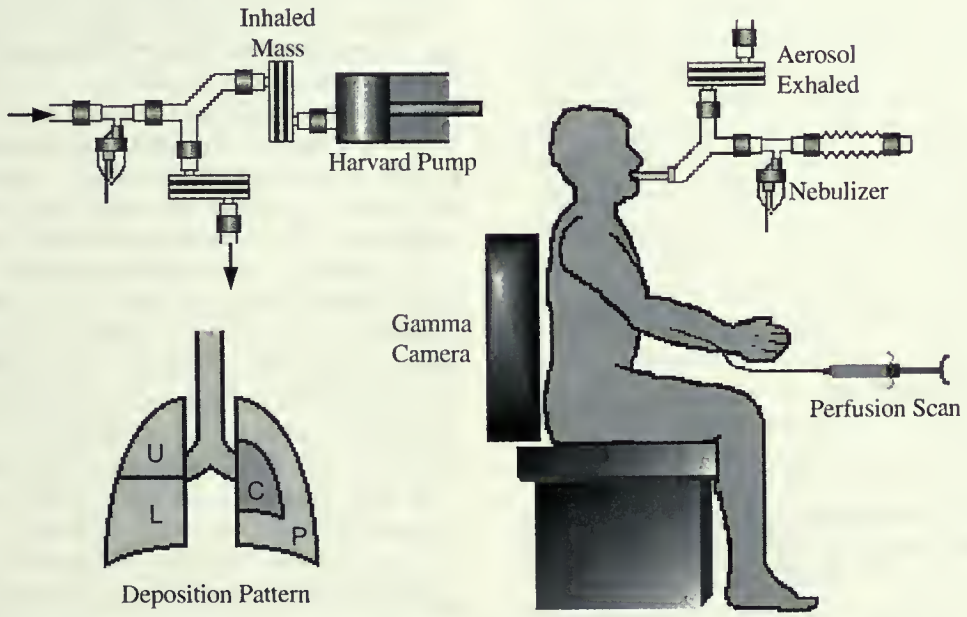

Fig. 3. Right: Diagram of gamma camera study designed to measure factors important in aerosol deposition: patient sitting in front of camera inhaling aerosol in a manner duplicating a typical clinical situation. Upper left: *Inhaled mass* is measured by filters and bench studies. Gamma camera can be calibrated via injection of macro-aggregates (perfusion scan). Lower left: Computerized regions of interest can be used to determine sites of deposition in the lung.

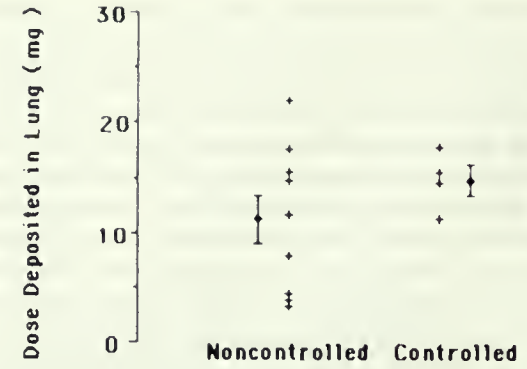

Fig. 4. Deposition of aerosol in controlled and noncontrolled breathing. Values are means ± SEM. The coefficient of variation was markedly reduced in the group with controlled breathing (18.6% versus 60.2%). (From Reference 11, with permission.)

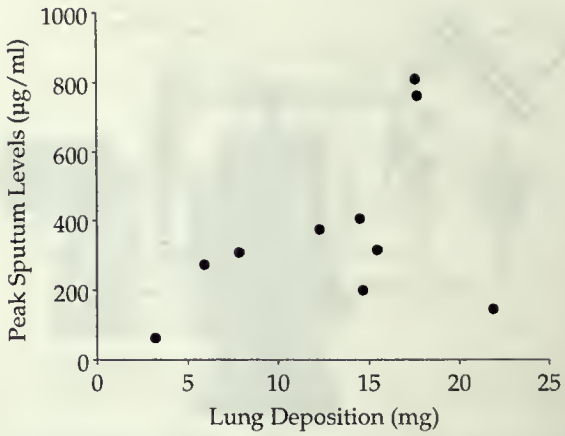

Fig. 6. Gentamicin levels in sputum versus lung deposition, from aerosolized gentamicin. (From Reference 11, with permission.)

estimated and quantified using the gamma camera by analysis of computer-generated regions of interest (Fig. 7). These regions defined the distribution of radioactivity in central and peripheral regions, the ratio of which (C/P) estimates the preference for particles to be deposited in central airways.[7,12] When normalized for regional lung volume, the C/P ratio indicates the tendency for deposition in large airways within the central lung region illustrated in Figure 7. Figure 8 shows the influence of this variable in analysis of secretions. In Figure 8, the sputum levels depicted in Figure 5 (peak levels) are divided by the milligram of gentamicin deposited in the patient (vertical axis). This value is plotted against the regional distribution of the deposited aerosol in the lung (C/P ratio). The good correlation observed demonstrates that peak sputum level is reasonably described by both the quantity of drug deposited and its initial distribution in the airways. Finally, the tendency of inhaled particles to deposit in the central airways was related to the degree of airway obstruction (Fig. 9). Patients with more airway obstruction had increased deposition in central airways.

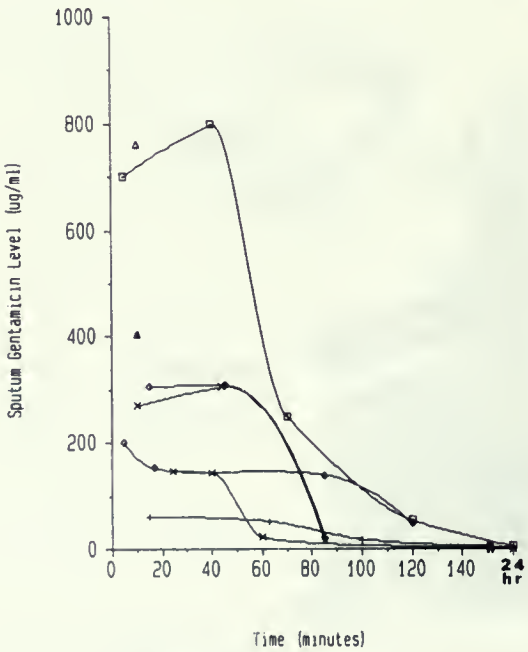

Fig. 5. Gentamicin levels in sputum versus time. Peak sputum levels averaged 307.5 ± 264 (SD) µg/mL and decreased rapidly over the next two hours. Two patients produced a single sample only. (From Reference 11, with permission.)

Subsequent clinical trials using tobramycin have found high levels of drug in expectorated sputum. Placebo-controlled trials have found improved spirometry and reduced frequency of hospitalization.[5] However, there have been no comparisons between aerosol therapy and systemic oral therapy in outpatients. In addition, the results of adjuvant therapy with aerosols have not been analyzed with respect to total and regional deposition. It is uncertain whether the results of previous trials are related to inadequacy of therapy, failure to penetrate peripheral airways, or the fact that sputum level per se does not predict efficacy.

In summary, in the ambulatory patient, our understanding of mechanisms of protection using aerosolized therapy remains incomplete. The availability of suitable oral antibiotics for the treatment of acute exacerbations of chronic bronchitis and bronchiectasis involving Gram-negative organisms has reduced the anecdotal use of aerosolized agents. In cystic fibrosis patients chronically colonized with these organisms, the use of aerosolized antibiotics, particularly tobramycin, has been beneficial. Further studies are necessary to define the role of these agents in patients with acute exacerbations requiring hospitalization.

The Intubated Patient

The intubated patient presents a different problem. In contrast to the patient with chronic bronchiectasis, most

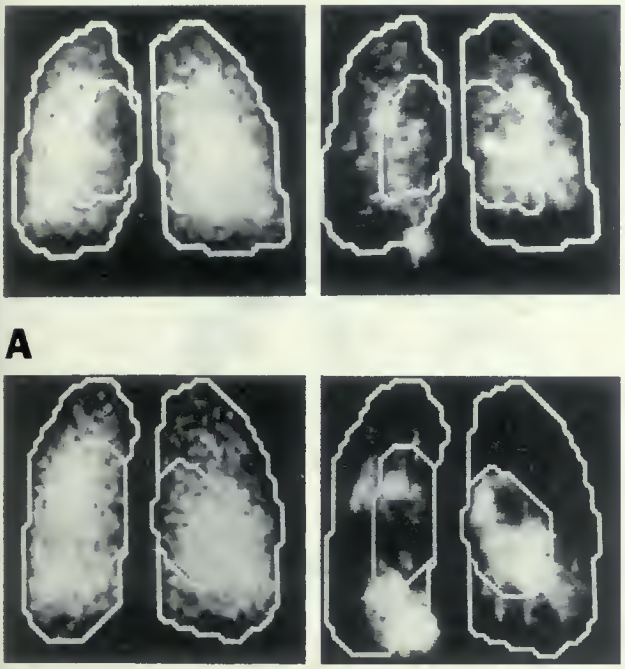

Fig. 7. Gamma camera images from two subjects with cystic fibrosis. Left: ^{133}Xenon equilibrium images, which define the outer lung regions as well as regional lung volume. Right: Deposition images following inhalation of radiolabeled gentamicin aerosol. Central regions of interest were drawn to encompass 30% of the total lung region. The distribution of radioactivity can be expressed as the ratio of activity in the central region to that in the peripheral region (C/P ratio). The aerosol pattern was normalized for volume by dividing the aerosol C/P by the xenon C/P. The ratio for subject A was 1.2. The ratio for subject B, with a more "central" distribution C/P, was 2.5. (From Reference 11, with permission.)

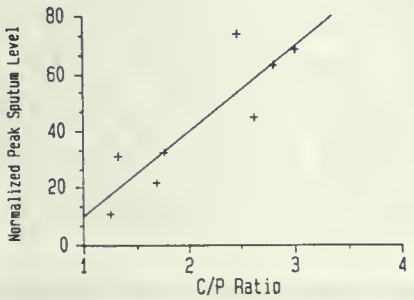

Fig. 8. Effect of site of deposition on sputum gentamicin level (in μg/mL). Sputum level, normalized for the amount deposited (μg/mL sputum divided by mL gentamicin deposited), is plotted against the ratio of activity in the central region to that in the peripheral region (C/P ratio). A significant correlation was obtained ($r = 0.888$, $p < 0.05$). (From Reference 11, with permission.)

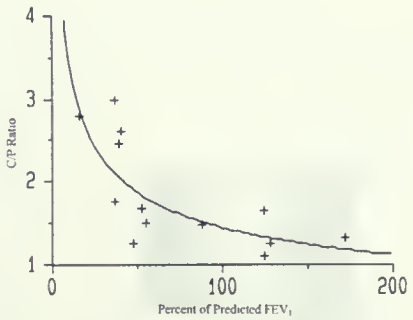

Fig. 9. Effect of pulmonary function on central deposition versus peripheral deposition. Forced expiratory volume in the first second (FEV_1) (as percent of predicted) is plotted against the ratio of activity in the central region to that in the peripheral region (C/P ratio). An exponential relationship was seen ($r = 0.76$, $p < 0.05$) (ie, the more obstructed the patient, as assessed by the forced expiratory volume in the first second, the more central the aerosol distribution. (From Reference 11, with permission.)

intubated patients (intubated without primary respiratory infection) initially have a relatively benign upper respiratory flora and limited evidence of lower respiratory tract infection. Once intubated, however, the flora of the upper respiratory tract changes. After several days, the airways become colonized with organisms considered more pathogenic. Many of these patients develop infection of the deep lung, with substantial mortality. While the process leading to the development of ventilator-associated pneumonia (VAP) is incompletely understood, it appears that enteric organisms from the gastrointestinal tract often colonize the oropharynx.[13] The presence of the endotracheal tube or tracheostomy may result in local inflammation, promoting infection in the intrapulmonary airways, which may lead to pneumonia. Additional factors, such as bacterial adherence, the use of systemic antibiotics, the local flora of a particular intensive care unit (ICU), and nutrition factors may be involved.[14] Once established, treatment of VAP with systemic antibiotics is usually effective. However, there are important associated toxicities. These toxicities may be related to the pneumonia itself, adverse effects of drugs, or to more prolonged residence in the ICU. They include *Clostridium difficile* toxicity in the lower gastrointestinal tract, renal failure, line sepsis, fungal overgrowth with systemic infection, and the development of bacterial resistance.

Mechanically ventilated patients are at greatest risk for pneumonia among hospitalized patients. Their risk is 6–21-fold greater than nonintubated patients.[15] The incidence of VAP ranges from 5% to 70% of all intubated patients, depending on the series. It is generally accepted that 7 days is the mean length of time for intubated patients to develop deep lung infection. The overall incidence is estimated to be 350,000 cases per year, with a mortality risk of 20–70%.[16–18]

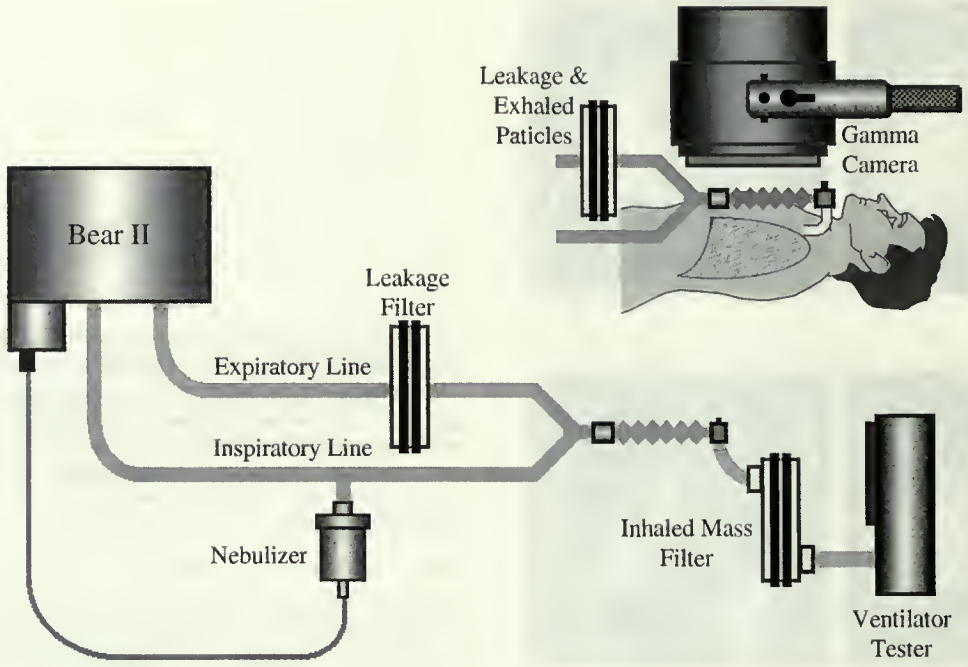

Fig. 10. Bench testing setup for aerosol delivery in patients maintained on mechanical ventilation. The principles are similar to those described in Figure 2. The setup duplicates the clinical delivery of aerosols with the *inhaled mass* determined by the inspiratory filter at the distal end of a tracheostomy tube or endotracheal tube. Using filters in the expiratory line, total aerosol deposition in patients can be determined. If the particles are radiolabeled, gamma camera images can be obtained as shown. (From Reference 30, with permission.)

The proposed path described above, of oral colonization leading to tracheobronchitis and pneumonia, has influenced several strategies to prevent deep lung infection. For example, selective decontamination of the digestive tract involves the attempt to eradicate organisms from the oropharynx and stomach using high-dose poorly-absorbed oral antibiotics. This approach has been controversial. Initial trials appeared to show some benefit in that the incidence of deep lung infection was reduced, with a possible reduction in mortality.[19–21] However, subsequent studies have not confirmed this observation in all patients.[22,23] In addition, the practice of using broad-spectrum antibiotics in all patients in the ICU can contribute to the development of resistance. Selective decontamination of the digestive tract is being investigated, and may be effective in post-trauma patients.[24] However, it is not universally practiced and is still considered experimental therapy.

The earliest studies on prevention of VAP used targeted topical therapy to the oropharynx. Using atomizers and poorly-absorbed Polymyxin antibiotics, intubated patients were treated prophylactically. This approach reduced Gram-negative infection in the deep lung secondary to susceptible organisms.[25] However, large clinical trials identified the emergence of resistant organisms and, ultimately, found no improvement in mortality.[26] The availability of systemic agents effective against Gram-negative organisms resulted in the discontinuance of this approach.

The failure of oropharyngeal atomization and the mixed results of its more extensive gastrointestinal counterpart, selective decontamination of the digestive tract, has led to the opinion that topical therapy in the prevention of VAP remains ineffective, and prophylaxis is not routinely recommended.[27] While disappointing, previous studies have, in general, involved the prophylactic treatment of all patients, and they have not used therapy directed primarily to the intrapulmonary airways and deep lung. Thus the potential utility of aerosolized antibiotics remains to be tested. The design of an appropriate study, however, has been limited by several basic difficulties. The first is the lack of a clinical indicator defining those patients who need prophylaxis to prevent VAP. The second is the reported difficulty in delivering aerosolized agents to the lungs of intubated mechanically ventilated patients.[28,29]

Measuring Aerosol Delivery in the Intubated Patient

Early studies measuring particle deposition in the lungs of intubated patients indicated that the efficiency of aerosol delivery was quite low (2–7%).[28] This was attributed to inherent inefficiencies of the nebulizer delivery system

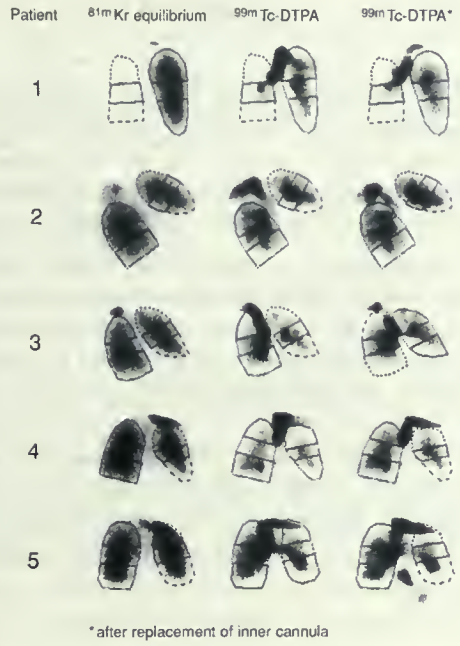

Fig. 11. Krypton equilibrium and technetium deposition images in 5 ventilator-dependent patients. Actual patient orientation is shown. The lung outline was determined by an ^{81m}Krypton equilibrium image (left column) and subsequently superimposed over the ^{99m}technetium-DTPA deposition images. Middle column: Deposition images obtained at ~100,000 counts/min after ~3–5 minutes of nebulization. Right column: Deposition images obtained immediately after the tracheotomy tube inner canula was replaced. The right lung outline for each patient was estimated from the chest radiograph. (From Reference 33, with permission.)

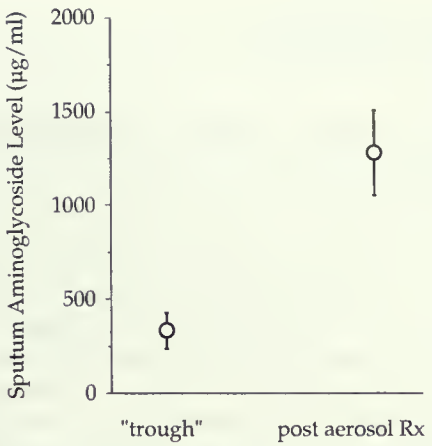

Fig. 12. Gentamicin sputum levels (means ± SD) obtained immediately prior to (left) and immediately following (right) aerosolized gentamicin nebulization in intubated patients receiving aerosol therapy every 8 hours. (From Reference 34, with permission.)

and the difficulty for particles to negotiate the endotracheal or tracheostomy tube.[29] However, by taking the same approach to nebulization via the ventilator as shown above for spontaneous breathing, the factors important to aerosol delivery using mechanical ventilation have been defined. As shown in Figure 10, the ventilator and its tubing (including the endotracheal tube) can be viewed as an extension of the nebulizer. Filters placed distal to the endotracheal (or tracheostomy) tube determine the *inhaled mass*, just as in Figure 2. Cascade impactors interposed in the circuit measure the MMAD of aerosols presented to the patient. Gamma camera imaging can be performed on intubated patients and, using filters, the dose to the patient and regional deposition to the lung can be determined using the same principles developed for spontaneously-breathing individuals. Over the last decade, serial in vitro and in vivo studies have determined the factors important in aerosol delivery during mechanical ventilation. Those factors include the nebulizer, the ventilator, the conditions of ventilation (eg, breathing pattern, humidification), and the position of devices in the circuitry.[30–32] These principles are now well described and, as will be shown below, it is now possible to develop efficiencies of aerosol delivery that exceed those previously reported in spontaneously-breathing patients.

It is possible to measure deposition in the intubated patient and to define regional distribution of drug in the lung. Figure 11 shows images from 5 tracheostomized patients maintained on long-term mechanical ventilation.[33] The left vertical column depicts ^{81m}krypton equilibrium images, which define regional ventilation. The other columns show aerosol images following inhalation of ^{99m}technetium-labeled aerosol. The images were obtained with the original tracheostomy tube in place (middle column) and with the tube changed (right column). This picture reveals qualitative information that demonstrates that if the lung is ventilated, particles do deposit within airways. Further, while the tubing captures particles, the amount of aerosol deposited in the tube is small, compared to lung deposition.[34] Studies of aerosolized antibiotics have revealed that significant amounts of aerosolized aminoglycoside can be deposited in the parenchyma of these patients and that levels of deposition during therapy can exceed those reported for spontaneously-breathing patients. Figure 12 shows the gentamicin levels of sputum suctioned from the airways of patients receiving aerosolized gentamicin (80 mg in the nebulizer every 8 h). In a "steady state" the trough level just prior to a treatment averaged about 300 µg/mL of sputum. Following therapy, levels approached 1,500 µg/mL. These levels are higher than those reported in Figure 5 and reflect the increased efficiency of aerosolized delivery in patients with an optimized ventilator/nebulizer system. Deposition averaged 22% of the original amount of drug placed in the nebulizer. This level of efficiency is more than double that reported for spontaneously-breathing cystic fibrosis patients (7.5%).[11,34]

Targeted Aerosol Prophylaxis in the Intubated Patient

A Human Model for Respiratory Infection: the Respiratory Care Unit. We have established a human model of Gram-negative infection in mechanically ventilated patients. This model is designed to study the process of colonization in the upper airway, using serial samples of secretions from patients who are clinically stable but instrumented and ventilated, living in the hospital. In this environment, serial assessment of these patients has allowed development of techniques for quantitating airway secretions,[35] maximizing aerosol delivery,[36] and defining potential indices for response, such as reduction in the volume of secretions, reduction in bacterial growth, and changes in inflammatory cytokines.[34] These variables may serve as potential surrogates for important clinical end points, such as reduction of VAP, mortality, and the incidence of resistant organisms. Early studies using this model found that aerosolized aminoglycosides delivered via ventilator can significantly reduce the volume of sputum quantitatively suctioned from the proximal airways of these patients. In addition, in the same patients, the growth of pathogenic bacteria is effectively suppressed. Consistent with the hypothesis that the instrumented patient develops associated inflammation in the proximal airways, we have found markedly elevated levels of inflammatory cytokines in the secretions. These include TNF-α, interleukin 1-β, soluble ICAM-1, and neutrophil elastase. These levels approach those seen systemically in patients with shock and acute respiratory distress syndrome. While their meaning in terms of clinical outcome remains obscure, we have shown that these levels correlate with the volume of secretions and that cytokine levels are reduced in concert with reduction in sputum volume following therapy with aerosolized antibiotics.[34]

The respiratory care unit patient or a step-down unit patient is clinically stable. Presently, it has been shown that antibiotics can be delivered to the intubated patient with measured effects. What is unclear is the clinical importance of any of these observations. To approach VAP and other ICU conditions, we have begun to study secretions in a similar manner in ICU patients. Early studies indicate that sputum volume can be quantitatively measured in the medical ICU. After 7 days in the unit, in patients without pneumonia as their initial diagnosis, a significant increase in secretions can be detected.[37] Follow-up studies will be designed to determine whether this increase in secretions serves as a useful predictor of clinical infection. If so, sputum volume may help define a targeted patient population to receive prophylactic aerosolized antibiotics.

Summary

Aerosolized antibiotic therapy appears to have potential for targeted therapy to the airways and deep lung to prevent VAP in patients at high risk for this disease. The definition of that high-risk population is important if this model is to be successful. We are attempting to define susceptible patients by measuring the volume of airway secretions, which mirrors the inflammation milieu of the central airways. Elevated sputum volume is marked by heavy growth of pathogenic organisms and high levels of inflammatory cytokines. Large-scale clinical trials are necessary to define the usefulness of these surrogates in defining a targeted population and for assessing the potential of aerosolized antibiotic prophylactic therapy for preventing pneumonia and mortality. If successful, the aerosol approach may avoid systemic therapy and its associated complications.

REFERENCES

1. Baran D, Dachy A, Klastersky J. Concentration of gentamicin in bronchial secretions of children with cystic fibrosis or tracheostomy. Int J Clin Pharmacol Biochem 1975;12(3):336–341.
2. Nolan G, McIvor P, Levison H, Fleming PC, Corey M, Gold R. Antibiotic prophylaxis in cystic fibrosis: inhaled cephaloridine as an adjunct to oral cloxacillin. J Pediatr 1982;101(4):626–630.
3. Hodson ME, Penketh ARL, Batten JC. Aerosol carbenicillin and gentamicin treatment of *Pseudomonas aeruginosa* infection in patients with cystic fibrosis. Lancet 1981;2(8256):1137–1139.
4. Stephens D, Garey N, Isles A, Levison H, Gold R. Efficacy of inhaled tobramycin in the treatment of pulmonary exacerbations in children with cystic fibrosis. Pediatr Infect Dis 1983;2(3):209–211.
5. Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. N Engl J Med 1999;340(1):23–30.
6. Brown RB, Kruse JA, Counts GW, Russell JA, Christou NV, Sands ML. Double-blind study of endotracheal tobramycin in the treatment of Gram-negative bacterial pneumonia. The Endotracheal Tobramycin Study Group. Antimicrob Agents Chemother 1990;34(2):269–272.
7. Smaldone GC, O'Riordan TG. Aerosol deposition and clearance. In: Wagner HN Jr. Principles of nuclear medicine, 2nd ed. Philadelphia: WB Saunders; 1995.
8. Determinants of dose and response to inhaled therapeutic agents in asthma. In: Schleimer R, Busse W, O'Byrne P, editors. Inhaled glucocorticoids in asthma: mechanisms and clinical actions. New York: Marcel Dekker; 1997.
9. O'Riordan TG, Smaldone GC. Aerosols. In: Adkinson NF Jr, Busse WW, Ellis EF, Middleton E Jr, Reed C, Yunginger JW Jr, editors. Allergy, principles and practices, 5th ed. St Louis: Mosby; 1998.
10. Smaldone GC. Drug delivery via aerosol systems: concept of "aerosol inhaled". J Aerosol Med 1991;4(3):229–235.
11. Ilowite JS, Gorvoy JD, Smaldone GC. Quantitative deposition of aerosolized gentamicin in cystic fibrosis. Am Rev Respir Dis 1987; 136(6):1445–1449.

12. Smaldone GC, Perry RJ, Bennett WD, Messina MS, Zwang J, Howite J. Interpretation of '24 hour lung retention' in studies of mucociliary clearance. J Aerosol Med 1988;1:11–20.
13. Johanson WG Jr, Pierce AK, Sanford JP, Thomas GD. Nosocomial respiratory infections with Gram-negative bacilli: the significance of colonization of the respiratory tract. Ann Intern Med 1972;77(5): 701–706.
14. Palmer LB. Bacterial colonization: pathogenesis and clinical significance. In: Niederman MS, editor. Clinics in chest medicine. Philadelphia: WB Saunders; 1987.
15. Guidelines for prevention of nosocomial pneumonia. Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 1997 Jan 3;46(RR-1):1–79.
16. Langer M, Mosconi PM, Cigada M, Mandella M. Long-term respiratory support and risk of pneumonia in critically ill patients. Intensive Care Unit Group of Infection Control. Am Rev Respir Dis 1989;140(2):302–305.
17. Fagon JY, Chastre J, Domart Y, Trouillet JL, Pierre J, Darne C, Gibert C. Nosocomial pneumonia in patients receiving continuous mechanical ventilation: prospective analysis of 52 episodes with use of a protected specimen brush and quantitative culture techniques Am Rev Respir Dis 1989;139(4):877–884.
18. Bassin AS, Niederman MS. Prevention of ventilator-associated pneumonia: an attainable goal? (review) Clin Chest Med 1995;16(1):195–208.
19. Unertl K, Ruckdeschel G, Selbmann HK, Jensen U, Forst H, Lenhart FP, Peter K. Prevention of colonization and respiratory infection in long-term ventilated patients by local antimicrobial prophylaxis. Intensive Care Med 1987;13(2):106–113.
20. Stoutenbeek CP, van Saene HFK, Miranda DR, Zandstra DF, Langrehr D. The effect of oropharyngeal decontamination using topical nonabsorbable antibiotics on the incidence of nosocomial respiratory tract infections in multiple trauma patients. J Trauma 1987;27(4): 357–364.
21. Pugin J, Aukenthaler R, Lew DP, Suter PM. Oropharyngeal decontamination decreases incidence of ventilator-associated pneumonia: a randomized, placebo controlled, double-blind clinical trial. JAMA 1991;265(20):2704–2710.
22. Gastinne H, Wolff M, Delatour F, Faurisson F, Chevret S. A controlled trial in intensive care units of selective decontamination of the digestive tract with nonabsorbable antibiotics. The French Study Group on Selective Decontamination of the Digestive Tract. N Engl J Med 1992;326(9):594–599.
23. Ferrer M, Torres A, Gonzalez J, Puig de la Bellacasa J, el-Ebiary M, Roca M, et al. Utility of selective digestive decontamination in mechanically ventilated patients. Ann Intern Med 1994;120(5):389–395.
24. Quinio B, Albanèse J, Bues-Charbit M, Viviand X, Martin C. Selective decontamination of the digestive tract in multiple trauma patients: a prospective double-blind, randomized, placebo-controlled study. Chest 1996;109(3):765–772.
25. Klick JM, du Moulin GC, Hedley-Whyte J, Teres D, Bushnell LS, Feingold DS. Prevention of Gram-negative bacillary pneumonia using polymyxin aerosol as prophylaxis. II. Effect on the incidence of pneumonia in seriously ill patients. J Clin Invest 1975;55(3):514–519.
26. Feeley TW, du Moulin GC, Hedley-Whyte J, Bushnell LS, Gilbert JP, Feingold DS. Aerosol polymyxin and pneumonia in seriously ill patients. N Engl J Med 1975;293(10):471–475.
27. Kollef MH. The prevention of ventilator-associated pneumonia (review). N Engl J Med 1999;340(8):627–634.
28. Fuller HD, Dolovich MB, Posmituck G, Pack WW, Newhouse MT. Pressurized aerosol versus jet aerosol delivery to mechanically ventilated patients: comparison of dose to the lungs. Am Rev Respir Dis 1990;141(2):440–444.
29. MacIntyre N, Silver RM, Miller CW, Schuler F, Coleman RE. Aerosol delivery to intubated, mechanically ventilated patients. Crit Care Med 1985;13(2):81–84.
30. O'Riordan TG, Greco MJ, Smaldone GC. Nebulizer function during mechanical ventilation. Am Rev Respir Dis 1992;145(5):1117–1122.
31. O'Riordan TG, Palmer LB, Smaldone GC. Aerosol deposition In mechanically ventilated patients: optimizing nebulizer delivery. Am J Respir Crit Care Med 1994;149(1):214–219.
32. Diot P, Morra L, Smaldone GC. Albuterol delivery in a model of mechanical ventilation: comparison of metered-dose inhaler and nebulizer efficiency. Am J Respir Crit Care Med 1995;152(4 Pt 1): 1391–1394.
33. Cabahug CJ, McPeck M, Palmer LB, Cuccia A, Atkins HL, Smaldone GC. Utility of technetium-99m-DTPA in determining regional ventilation. J Nucl Med 1996;37(2):239–244.
34. Palmer LB, Smaldone GC, Simon SR, O'Riordan TG, Cuccia A. Aerosolized antibiotics in mechanically ventilated patients: delivery and response. Crit Care Med 1998;26(1):31–39.
35. Palmer LB, Smaldone GC, Simon S, O'Riordan T, Morra L. Tracheal aspirates in long-term mechanically ventilated patients: a human model of Gram-negative infection and airway inflammation. Chest 1995;108(5):1326–1332.
36. Diot P, Morra L, Smaldone GC. Albuterol delivery in a model of mechanical ventilation: comparison of metered-dose inhaler and nebulizer efficiency. Am J Respir Crit Care Med 1995;152(4 Pt 1): 1391–1394.
37. Palmer L, Smaldone GC. Targeting pneumonia in the ICU: secretion volume (abstract). Am J Respir Crit Care Med 2000;161(3)A92.

Aerosolized Medications for Altering Lung Surface Active Properties

Neil R MacIntyre MD FAARC

Introduction
Surface Active Properties
Diseases with Altered Surface Active Properties
Surface Active Substances Available for Exogenous Administration
Instilled Surfactant Therapy
Aerosolized Surfactant Therapy
Other Issues with Aerosolized Surfactants
Surface Active Materials Other Than Surfactant
Summary
[Respir Care 2000;45(6):676–683] *Key words: aerosol, surface active properties, surfactant, surface active material.*

Introduction

Aerosol inhalation is an effective way to deliver medications into the lung (eg, bronchodilators and steroids). Surface active material might also be effectively delivered by aerosol into lungs with altered surface active properties. This article addresses this concept by reviewing the following topics: surface active properties of the lung; diseases that alter these properties; therapeutic surfactants; instillation techniques; aerosol techniques; other aspects of surfactant aerosolization; and surface active materials other than surfactant.

Surface Active Properties

Normal lung expansion is accomplished by inspiratory muscle contraction generating a negative pleural pressure that, in turn, inflates the lung. Lung mechanical properties that resist inflation include the inherent elasticity of lung tissue and the airway resistance. An important feature in all mammalian lungs is the presence of surface active lining material in the alveoli. This material consists of a variety of phospholipids, the most common being dipalmitoyl phosphatidyl choline.[1,2] This material is naturally associated with a number of proteins (SP-A,B,C,D) that facilitate spreading and have anti-inflammatory effects. Together, these materials greatly reduce the surface tension of the alveolar membrane and, as a consequence, allow the lung to inflate with relatively small transpulmonary pressure generation. In Figure 1, a lung with surface active material is compared to a lung without this material. Note the much higher pressure requirements (and thus lower calculated compliance) that result when the surface active material is not present or not functioning properly.

Diseases with Altered Surface Active Properties

There are two fundamentally different types of diseases that involve surfactant dysfunction. The first category is surfactant depletion syndromes. The second category is surfactant dysfunction syndromes.[3,4]

In humans, surfactant depletion syndromes usually involve premature infants. In the normal human neonate at birth, as much as 50–100 mg/kg of surfactant are present in the lungs.[3] This material spreads with the first breath and properly establishes the appropriate surface tension necessary for normal ventilation. In the premature infant, the amount of surfactant can be markedly reduced. Indeed, in severe respiratory distress syndrome (RDS), the surfactant amount is generally < 5 mg/kg, and the recoil pressures of the lungs are so high that many units either do not open or else collapse during expiration. This leads to shunt,

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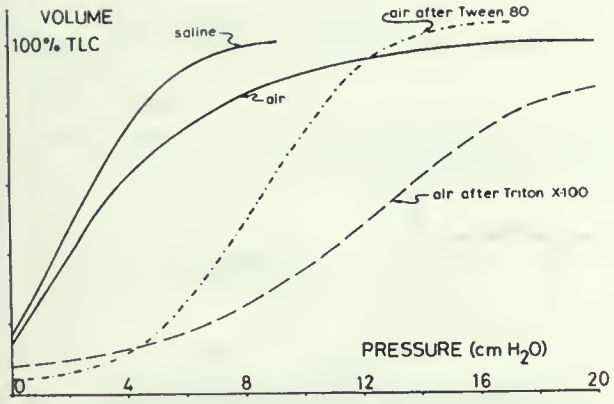

Fig. 1. Pressure-volume plot illustrating effect of surface active material on lung mechanical properties. The solid line represents the pressure-volume relationships of a normal lung. The dashed line represents the pressure-volume relationship of a lung in which surface active material has been destroyed by a detergent. Note the severe worsening of lung compliance when surfactant is not present. (From Hoppin FG, et al. Lung recoil. In Macklem P, Mead J. Handbook of physiology. Bethesda: American Physiologic Society; 1986: 195–216, with permission.)

hypoxemia, right ventricular dysfunction, and, potentially, death.

Diseases involving dysfunctional surfactant include many adult respiratory disorders (eg, acute respiratory distress syndrome [ARDS], pneumonia, interstitial lung disease).[4] In the normal adult lung, the surfactant pool is less than in the neonate, generally in the range of 5–15 mg/kg. In these disease states, the absolute amount of phospholipid may actually be normal (or even elevated). However, surfactant properties are often disrupted by inflammatory mediators, and there are disturbed surfactant metabolism and recycling phenomena. Figure 2 illustrates the time course of abnormal surfactant behavior in adults with trauma-related acute lung injury.

Administering surfactant might benefit surfactant depletion syndrome and surfactant dysfunction syndrome. One might anticipate greater efficacy, however, from surfactant administration in a depletion syndrome, where surfactant is supplying simple replacement, as compared to surfactant administration in a surfactant dysfunction syndrome involving more complex processes. Indeed, as discussed in more detail below, this has been the case in a number of clinical studies performed in the last 20 years.

Surface Active Substances Available for Exogenous Administration

Over the past 20 years a variety of different surfactants have been developed (Table 1).[1–4] A number of these are so-called natural surfactants in that they come from lavage of animal lungs (eg, porcine or bovine surfactants). An advantage to this type of surfactant is that many of the surface active-related proteins are also present.

It is also possible to manufacture various phospholipids that have surface active lowering properties. The most widely used of these is simple dipalmitoyl phosphatidyl choline (Exosurf). An obvious disadvantage to these simple phospholipids is that they lack the surface active-related proteins of natural surfactants. In recent years, however, these simple phospholipids have been combined with genetically engineered surface active-related proteins to create a synthetic surfactant that has more properties comparable to the natural surfactants.

Nonphospholipid substances can also have surface active lowering properties. A class of drugs that has created considerable interest is perfluorocarbon and the specific compound perflubron.[5,6] These compounds are interesting in that they are highly oxygen soluble and can actually replace gas in the alveolar space. Although perflubron can be used to provide total ventilation, most current studies focus on the use of perflubron only to replace gas in the functional residual capacity. Under these circumstances, perflubron thus functions as "liquid positive end-expiratory pressure" to recruit alveoli (Fig. 3) and substantially reduce lung recoil pressures.

Surfactant can be administered in a variety of ways (Table 2). Direct instillation is the simplest, but transient gas exchange and hemodynamic effects can occur during the procedure ("fluid bolus" effect: Fig. 4).[7,8] In addition, distribution of instilled fluid follows gravity, which may or may not be optimal. An alternative approach is to aerosolize the surfactant with jet or ultrasonic devices.[9–12] Aerosol delivery to the lungs is always going to be less than with direct instillation, simply because aerosol is wasted in ventilator circuitry and upper airway deposition.[13] Lung delivery of an aerosol can be further reduced if particle sizes are too large (ie, > 5 μm mass median aerodynamic diameter), if aerosol delivery is not coordinated with a slow inspiration and breath-hold, or if airways (especially artificial airways) are long and narrow.[13] Indeed, estimates of lung delivery of aerosolized surfactant are generally $< 10\%$ of delivered dose,[14–17] although under conditions where particle sizes are small and artificial airways are short and wide, this may be several-fold higher.[7,18] Despite this reduced delivery, advantages of the aerosol route include a reduced "fluid bolus" effect and the ability to provide continuous dosing. Also, aerosolized surfactant distributes according to ventilation[12,16] and, thus, its distribution to various lung units will differ from the gravity-dependent distribution of instilled surfactant. Depending on regional lung mechanical properties, this different distribution effect may or may not have gas exchange or mechanical advantages over the direct instillation technique. It is also possible to combine these approaches (ie, use an initial instillation and then follow it with an aerosol).

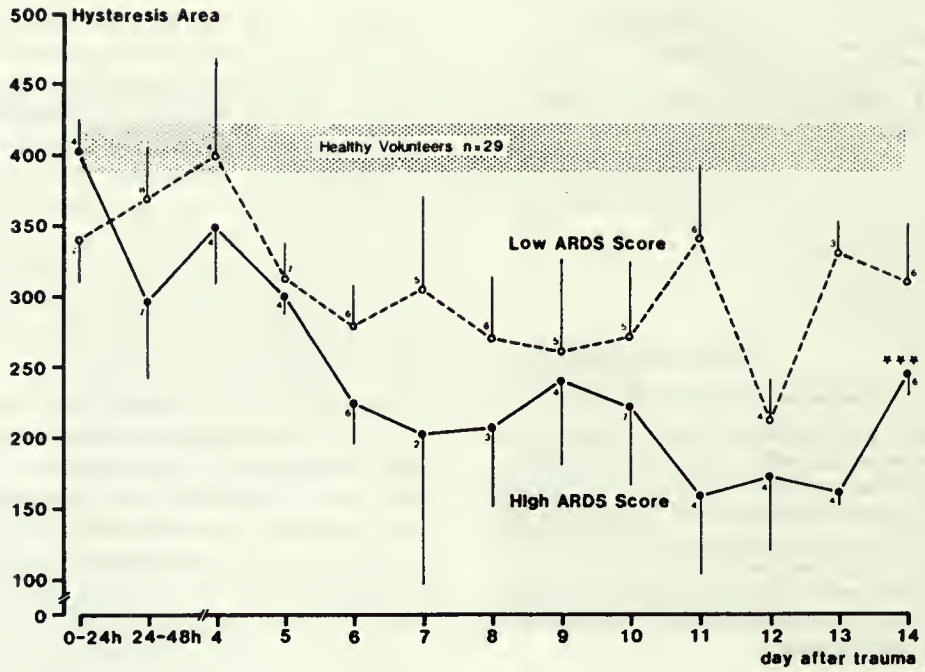

Fig. 2. Time course of surfactant abnormalities in mild/moderate (dashed lines) and severe (solid lines) acute lung injury. On the vertical axis is plotted surface active function (hysteresis area of alveolar lavage fluid). On the horizontal axis is plotted time after initiation of injury. The shaded area depicts normal reference values. Note that important abnormalities in lung surface active properties correlate with the degree of lung injury and can persist for several weeks before recovering. (From Reference 4, with permission.)

Table 1. Surfactants Available for Clinical Use

Natural
Bovine (Survanta, Infasurf, Alveofact)
Porcine (Curosurf)
Synthetic
With proteins (KL4, Venticute)
Without proteins (Exosurf)

Instilled Surfactant Therapy

The benefits of surfactant replacement were first demonstrated in animal models of infant RDS, using direct instillation.[19,20] The first clinical use of surfactant in RDS was in 1980, and also used the instilled approach.[21] Since then, a number of clinical trials have demonstrated that instillation of both natural and synthetic surfactants into premature infants with RDS dramatically improves lung mechanics, gas exchange, and outcome (Fig. 5).[1]

Standard therapy today for RDS generally involves instilling bolus doses of ≥ 100 mg/kg (a full "replacement" dose). With instillation, 100% of the dose enters the airway. However, because instilled surfactant distributes by gravity, the instillation should be followed by turning the infant to achieve effective distribution.[1,3] As noted above, one of the problems with bolus instillation is that the necessary 4–5 mL/kg fluid loads into the airway can have substantial airway and hemodynamic effects in the neonate, so careful monitoring of vital signs and appropriate oxygen supplementation is important.

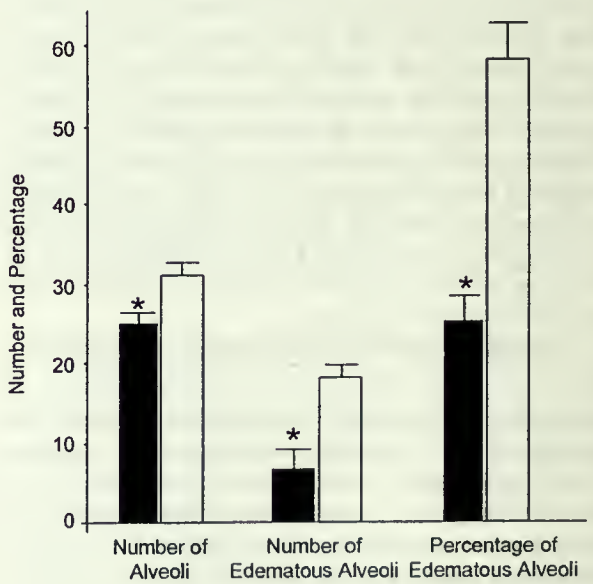

Fig. 3. Effect of instilled perflubron on lung properties in an animal model of acute lung injury. The open bars are gas-ventilated animals, the shaded bars are perflubron-ventilated animals (30 mL/kg perflubron). (From Reference 5, with permission.)

Table 2. Surfactant Delivery Techniques

Instillation
Single or multiple
Preceded by lavage
Aerosol
Alone
Preceded by instillation
Accompany multiple instillations

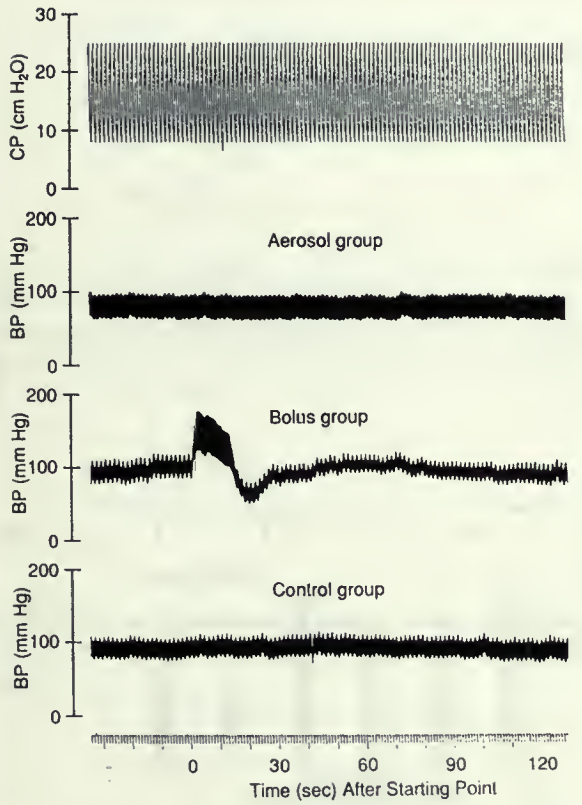

Fig. 4. Effects of a bolus administration of instilled surfactant (5 mL/kg) in an animal model of acute lung injury. Plotted are ventilator circuit pressures (top panel), airway pressures during aerosolized surfactant (second panel), airway pressures during bolus surfactant (third panel), and control (bottom panel). Surfactant administration occurred at time zero. Note that the bolus instillation was associated with substantial hemodynamic effects. (From Reference 8, with permission.)

Because of the success of surfactant replacement therapy in neonates, a number of investigations have attempted to duplicate this success in adult lung injury (eg, ARDS). As noted above, however, in adult lung injury, surfactant dysfunction rather than depletion is usually the issue, so simple replacement strategies that are effective in the premature neonate may not be adequate in adults.

Despite this, promising animal and human studies using instilled surfactant in acute lung injury/ARDS have been reported. Animal models[8,17,22] have included sheep, rats, and rabbits. In short-term studies, instillation of "infant replacement" doses (eg, $\geq$ 100 mg/kg) has usually shown improved gas exchange and lung mechanics. Similar results have been observed in small human trials.[22–25] In the study by Gregory et al,[23] pharmacologic doses of 4 boluses of 100 mg/kg surfactant seemed to improve gas exchange and perhaps survival in a small group of patients. More impressive was the study by Walmrath et al,[24] who used bronchoscopic instillation of $\leq$ 300 mg/kg surfactant and found quite substantial improvement in gas exchange and lung mechanics (Fig. 6). As of this writing, several other clinical trials are underway investigating the use of instilled surfactant in ARDS. One of these trials involves simple bolus techniques through the endotracheal tube. Another, however, uses a more complex approach, which involves first lavaging each segment of the lung with the surfactant and then filling it with additional surfactant.

Aerosolized Surfactant Therapy

It is interesting that the first attempts at replacing surfactant in the premature neonate were by the aerosol route.[1,26] The original intent with using the aerosol route was to reduce the effects of the fluid bolus on gas exchange and hemodynamics and to perhaps improve distribution. However, inefficient aerosol systems, coupled with the difficulty in delivering aerosols through an endotracheal tube, made these initial attempts unsuccessful. When the ease and effectiveness of surfactant instillation was subsequently demonstrated, interest waned for using aerosolized surfactant in the premature infant.

Recent animal work with improved aerosol delivery systems suggests that the aerosol route may still be a viable alternative in the premature infant.[7,16,27,28] Moreover, the gas exchange and mechanics benefits seen with the aerosol approach were comparable to those seen with the instillation technique, but required only a fraction of the conventional 100 mg/kg instilled dose (Table 3). Given that airway delivery of an aerosol is always going to be less than with a bolus instillation, especially through narrow artificial airways, it is remarkable that aerosol delivery can be so effective. One reason for this may be the distribution. Specially, as noted above, instilled doses tend to follow gravity, whereas aerosolized doses follow ventilation. Although this may result in inhomogeneous distribution,[16] one might speculate that this could be more beneficial in delivering surfactant to the peripheral regions that need it most. Another issue related to aerosolized delivery is the absence of the "bolus" effect.[8] Finally, a slower, more continuous administration from an aerosol may facilitate spreading of the material or help to penetrate more slowly recruitable lung units.

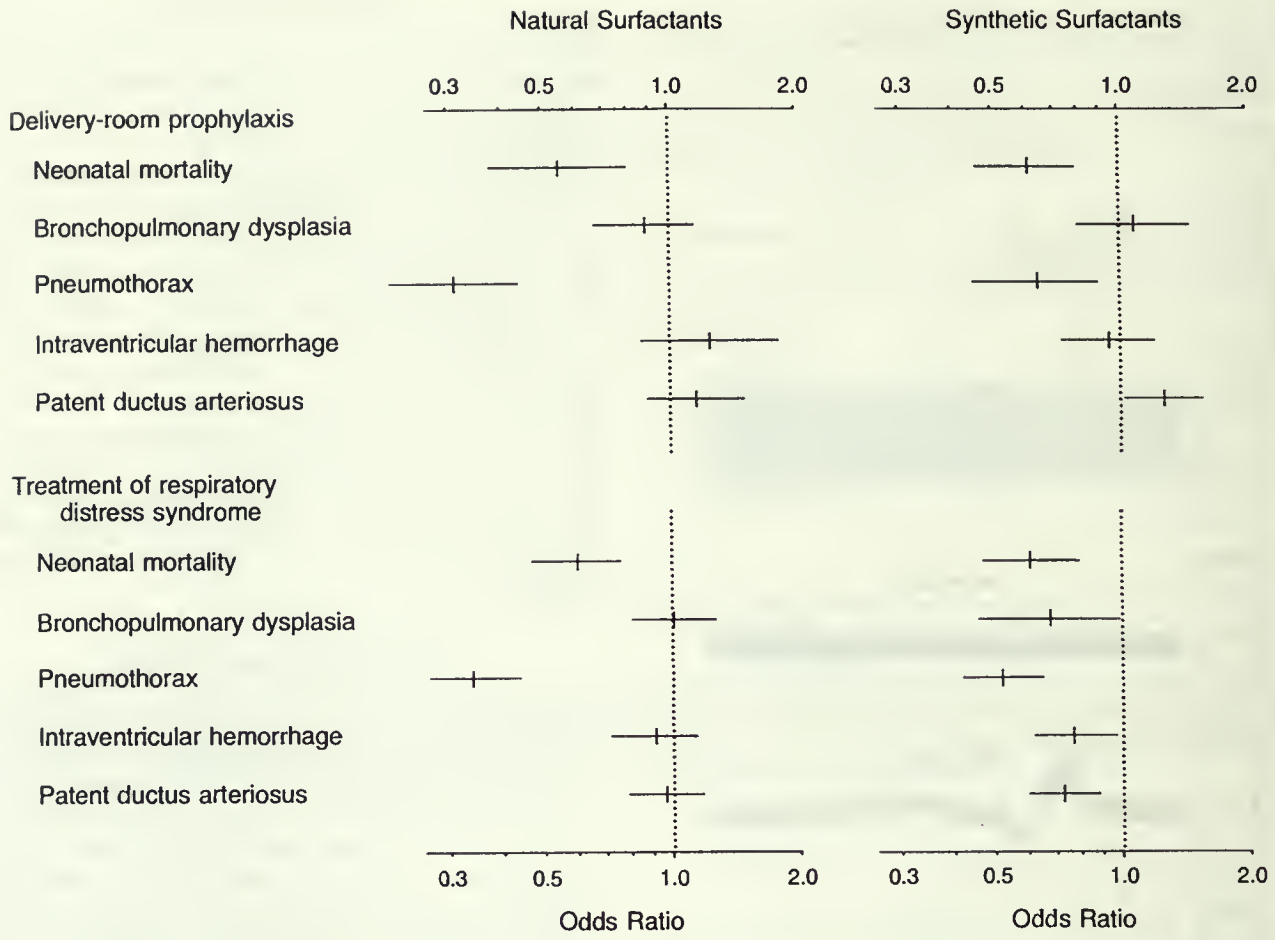

Fig. 5. Odds ratios from 4 meta-analyses of controlled studies showing benefit from instilled surfactant in premature infants with RDS. The 95% confidence intervals are plotted. Ratios to the left of zero favor surfactant treatment. (From Reference 1, with permission.)

Aerosol delivery of surfactant has also been studied in animal models of adult acute lung injury.[8,17,18,22,29,30] As in the premature infant, total delivery from an aerosol to the lungs is always going to be less than with instillation, especially in the presence of an endotracheal tube. Nevertheless, in a variety of animal models, aerosolized surfactant has been shown to provide important gas exchange and mechanics effects comparable to instilled surfactant (Figs. 7 and 8). Unlike the surfactant depletion syndromes, however, the surfactant dysfunction syndromes of acute lung injury seem to require aerosolized doses more comparable to that of the instilled dose (Table 4).

To date, only one randomized trial of aerosolized surfactant has been performed in adults with acute lung injury: the multicenter Exosurf trial.[31] In this study, patients with ARDS were randomized to receive either aerosolized surfactant or aerosolized saline for 5 days. Over 700 patients were randomized, but the trial was stopped because it became clear that the aerosolized surfactant had no benefit. Two major concerns surround this trial and its conclusion that aerosolized surfactant is ineffective. First, the

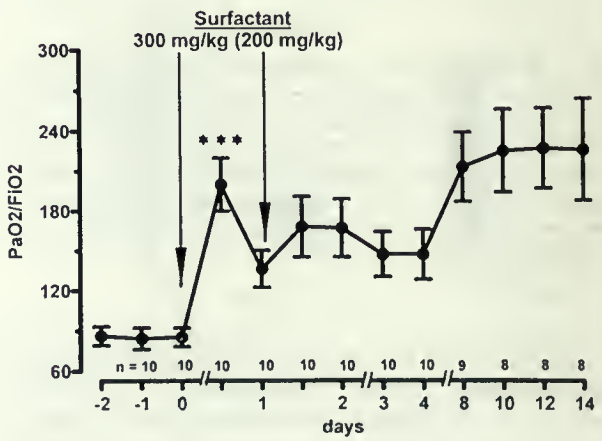

Fig. 6. Effects of bronchoscopically instilled surfactant on arterial partial pressure of oxygen (P_{aO_2}) in adult humans with ARDS. F_{IO_2} = fraction of inspired oxygen. *** = $p < 0.001$ for comparison of the P_{aO_2}/F_{IO_2} values before and after first surfactant application. (From Reference 24, with permission.)

Table 3. Aerosolized Surfactant in Animal Models of Surfactant Depletion Syndromes

Author (year)	Animal Model	Dose	Outcome(s)
Lewis et al (1991)[27]	Premature lambs	2 mg/kg over 120–180 min	Improved mechanics
Li et al (1994)[28]	Lavaged rats	75 mg/kg over 60 min	Improved mechanics and gas exchange
Lewis et al (1993)[16]	Lavaged sheep	8 mg/kg over 180 min	Improved mechanics and gas exchange
Schermuly et al (1997)[7]	Detergent rats	18 mg/kg over 120 min	Improved gas exchange

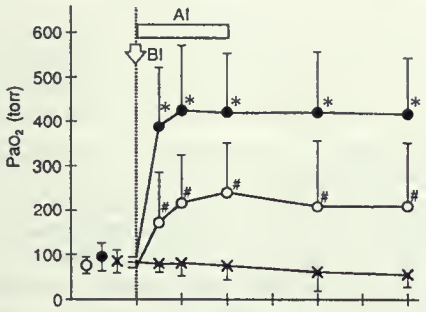

Fig. 7. Arterial partial pressure of oxygen (P_{aO_2}) response to surfactant therapy in endotoxin-induced acute respiratory distress syndrome in rats. Animals were treated with either a surfactant instillation (BI, solid circles), aerosolized surfactant (AI) open circles), or served as controls (x). (From Reference 8, with permission.)

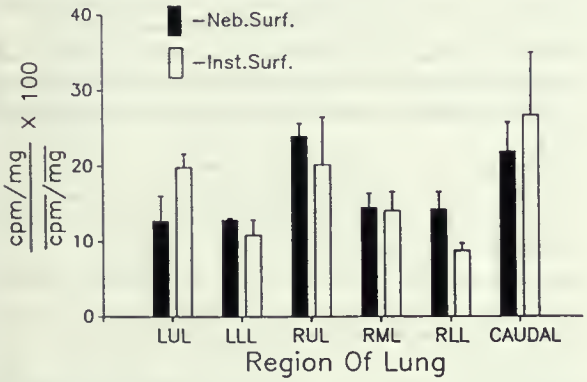

Fig. 8. Distribution of aerosolized (closed bars) versus instilled (open bars) surfactant in a saline lavage sheep model of acute lung injury. On the vertical axis is relative deposition and on the horizontal axis are lobar lung regions. Distribution of surfactant is clearly different with the two techniques. LUL = left upper lung. LLL = left lower lung. RUL = right upper lung. RML = right middle lung. RLL = right lower lung. (From Reference 16, with permission.)

surfactant used was simple dipalmitoyl phosphatidyl choline, an artificial surfactant without any surface active proteins. As noted above, this is a serious concern in adults, who suffer surfactant dysfunction syndrome rather than surfactant depletion syndrome. Under these circumstances, the surfactant-related proteins may be particularly important both for maximizing surfactant function and in providing anti-inflammatory effects. A second concern is that the aerosol-generating system used in this trial was very ineffective in terms of delivery to lung parenchyma. In a study using radioactive tracers, it was shown that < 5% of the aerosolized material actually made it into the lung.[14] Because of these two serious concerns, it is probably premature to conclude that aerosolized surfactant in adult lung injury is ineffective.

Other Issues with Aerosolized Surfactants

A number of studies have tried to combine aerosolized surfactant with high-frequency ventilation in the infant with RDS. This interesting ventilatory pattern (high velocity gas flow hundreds of times per minute) may help aerosol distribution and, in at least one study in premature infants, the high-frequency approach coupled with aerosolized surfactant had better oxygenation and blood pressure effects than the instillation method.[32]

Aerosolized surfactants have also been tried in airway diseases.[33–35] The rationale behind this is that surfactant in the airways plays an important role in mucus function and airway clearance properties. In two small studies involving cystic fibrosis and chronic bronchitis patients, aerosolized surfactant did not show benefit. In a more appropriately powered larger study,[35] however, two weeks of aerosolized surfactant treatments to outpatients with chronic bronchitis did show improvement in airway function and mucus properties.

An improved delivery system might increase the utility of aerosolized surfactants. As noted above, there may be reasons why the aerosolized route would be preferable to the instilled route. If the deposition could be further improved, especially in patients with endotracheal tubes, the aerosol route might be shown to be a much more cost-effective way of delivering surfactants. One such approach might be the use of intra-airway aerosol delivery system using either jet nebulizers or ultrasonic systems.[36]

Surface Active Materials Other Than Surfactant

There are surface active materials other than surfactants. In recent years, perfluorocarbon instillation has been studied as a way of recruiting injured/gasless alveoli and improving lung mechanics and gas exchange.[5,6] Indeed, instilled perflubron has in a number of studies been shown to improve gas exchange and lung mechanical function when

Table 4. Aerosolized Surfactant in Animal Models of Surfactant Dysfunction Syndromes

Author (year)	Animal Model	Dose	Outcome(s)
Zelter et al (1990)[29]	Oleic acid sheep	45 mg/kg over 300 min	Reduced lung water on rechallenge
Lewis et al (1991)[17]	NNNMU rabbits	120 mg/kg over 180 min	Improved mechanics
Huang et al (1995)[18]	Oxygen toxic baboons	—	Improved gas exchange
Widner et al (1996)[22]	Kerosene sheep	90 mg/kg over 360 min	Improved mechanics and gas exchange
Tashiro et al (1996)[8]	Endotoxin rats	800 mg/kg over 60 min	Improved gas exchange
Lutz et al (1998)[30]	Endotoxin pigs	40 mg/kg over 240 min	Improved gas exchange

NNNMU = N-nitroso-N-methylurethane

large (eg, full functional residual capacity of 30 mL/kg) fluid volumes are used.[5,6] However, to date there have been no studies of the aerosol route for these particular substances.

Summary

Surface active material is important in the function of both the infant and adult lung. In the premature infant, surfactant depletion results in the requirement for very high distending pressures to open alveoli. As a consequence, shunt, hypoxemia, and right ventricular dysfunction occur. Surfactant replacement, especially by the direct instillation approach, has been proven effective in improving clinical outcome under these circumstances. Problems with surfactant instillation include the "fluid bolus" effect and concerns about optimal distribution of the instilled material. Recent improvements in aerosol systems have created interest in using aerosol delivery to reduce the total dose of surfactant required to treat RDS.

In adult acute lung injury, surfactant dysfunction, rather than depletion, is the problem. Simple phospholipid replacement strategies thus may not be effective. Instead, surfactant delivery strategies aimed at regional targeting with surfactants having the necessary associated proteins may be the goal in ARDS. In adults, several instillation trials are underway, but there is also a hope that an aerosol strategy might also be tried. The aerosol route may be particularly useful if a high-efficiency aerosol system (eg, one distal to an endotracheal tube) can be shown to be effective.

Other surface active materials exist and there are small studies showing benefit when large instilled doses of these materials are given. These materials, however, have never been studied as aerosols.

REFERENCES

1. Jobe AH. Pulmonary surfactant therapy (review). N Engl J Med 1993;328(12):861–868.
2. Rider ED. Metabolism of pulmonary surfactant. Semin Respir Crit Care Med 1995;16:17–28.
3. Allred TF, Auten RL. Surfactant therapy in newborns. Semin Respir Crit Care Med 1995;16:3.
4. Pison U, Seeger W, Buchhorn R, Joka T, Brand M, Obertacke U, et al. Surfactant abnormalities in patients with respiratory failure after multiple trauma. Am Rev Respir Dis 1989;140(4):1033–1039.
5. Quintel M, Heine M, Hirschl RB, Tillmanns R, Wessendorf V. Effects of partial liquid ventilation on lung injury in a model of acute respiratory failure: a histologic and morphometric analysis. Crit Care Med 1998;26(5):833–843.
6. Fuhrman BP, Paczan PR, DeFrancisis M. Perfluorocarbon-associated gas exchange. Crit Care Med 1991;19(5):712–722.
7. Schermuly R, Schmehl T, Gunther A, Grimminger F, Seeger W, Walmrath D. Ultrasonic nebulization for efficient delivery of surfactant in a model of acute lung injury: impact on gas exchange. Am J Respir Crit Care Med 1997;156(2 Pt 1):445–453.
8. Tashiro K, Yamada K, Li WZ, Matsumoto Y, Kobayashi T. Aerosolized and instilled surfactant therapies for acute lung injury caused by intratracheal endotoxin in rats. Crit Care Med 1996;24(3):488–494.
9. Ikegami M, Hesterberg T, Nozaki M, Adams FH. Restoration of lung pressure-volume characteristics with surfactant: comparison of nebulization versus instillation and natural versus synthetic surfactant. Pediatr Res 1977;11(3 Pt 1):178–182.
10. Dijk PH, Heikamp A, Piers DA, Weller E, Oetomo S. Surfactant nebulisation: safety, efficiency and influence on surface lowering properties and biochemical composition. Intensive Care Med 1997; 23(4):456–462.
11. Ellyett KM, Broadbent RS, Fawcett ER, Campbell AJ. Surfactant aerosol treatment of respiratory distress syndrome in the spontaneously breathing premature rabbit. Pediatr Res 1996;39(6):953–957.
12. Henry MD, Rebello CM, Ikegami M, Jobe AH, Langenback EG, Davis JM. Ultrasonic nebulized in comparison with instilled surfactant treatment of preterm lambs. Am J Respir Crit Care Med 1996; 154(2 Pt 1):366–375.
13. Aerosol consensus statement—1991. American Association for Respir Care. Respir Care 1991;36(9):916–921.
14. MacIntyre NR, Coleman RE, Schuller FS, Zaccardelli D, Pattishall E. Efficiency of the delivery of aerosolized surfactant to intubated patients with the adult respiratory distresss syndrome (abstract). Am Rev Respir Dis 1994;149(4 Pt 2):A125
15. Fok TF, al-Essa M, Dolovich M, Rasid F, Kirpalani H. Nebulisation of surfactants in an animal model of neonatal respiratory distress. Arch Dis Child Fetal Neonatal Ed 1998;78(1):F3–F9.
16. Lewis JF, Tabor B, Ikegami M, Jobe AH, Joseph M, Absolom D. Lung function and surfactant distribution in saline-lavaged sheep given instilled vs. nebulized surfactant. J Appl Physiol 1993;74(3): 1256–1264.

17. Lewis J, Ikegami M, Huguchi R, Jobe A, Absolom D. Nebulized vs. instilled exogenous surfactant in an adult lung injury model. J Appl Physiol 1991;71(4):1270–1276.
18. Huang YC, Sane AC, Simonson SG, Fawcett TA, Moon RE, Fracica PJ, et al. Artificial surfactant attenuates hyperoxic lung injury in primates. I. Physiology and biochemistry. J Appl Physiol 1995;78(5): 1816–1822.
19. Enhornig G, Robertson B. Lung expansion in the premature rabbit fetus after tracheal deposition of surfactant. Pediatrics 1972;50(1): 58–66.
20. Robertson B, Enhorning G. The alveolar lining of the premature newborn rabbit after pharyngeal deposition of surfactant. Lab Invest 1974;31(1):54–59.
21. Fujiwara T, Maeta H, Chida S, Morita T, Watabe Y, Abe T. Artificial surfactant therapy in hyaline-membrane disease. Lancet 1980; 1(8159):55–59.
22. Widner LR, Goodwin SR, Berman LS, Banner MJ, Freid EB, McKee TW. Artificial surfactant for therapy in hydrocarbon-induced lung injury in sheep. Crit Car Med 1996;24(9):1524–1529.
23. Gregory TJ, Steinberg KP, Spragg R, Gadek JE, Hyers TM, Longmore WJ, et al. Bovine surfactant therapy for patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 1997; 155(4):1309–1315.
24. Walmrath D, Gunther A, Ghofrani HA, Schermuly R, Schneider T, Grimminger F, Seeger W. Bronchoscopic surfactant administration in patients with severe adult respiratory distress syndrome and sepsis. Am J Respir Crit Care Med 1996;154(1):57–62.
25. Haslam PL, Hughes DA, MacNaughton PD, Baker CS, Evans TW. Surfactant replacement therapy in late-stage adult respiratory distress syndrome. Lancet 1994;343(8904):1009–1011.
26. Robillard E, Alarie Y, Dagenais-Perusse P, Baril E, Guilbeault A. Microaerosol administration of synthetic β-γ-dipalmitoyl-L-α-lecithin in the respiratory distress syndrome: a preliminary report. Can Med Assoc J 1964;90:55–57.
27. Lewis JF, Ikegami M, Jobe AH, Tabor B. Aerosolized surfactant treatment of preterm lambs. J Appl Physiol 1991;70(2):869–876.
28. Li WZ, Chen WM, Kobayashi T. Aerosolized surfactant reverses respiratory failure in lung-lavaged rats. Acta Anaesth Scand 1994; 38(1):82–88.
29. Zelter M, Escudier BJ, Hoeffel JM, Murray JF. Effects of aerosolized artificial surfactant on repeated oleic acid injury in sheep. Am Rev Respir Dis 1990;141(4 Pt 1):1014–1019.
30. Lutz C, Carney D, Finck C, Picone A, Gatto LA, Paskanik A, et al. Aerosolized surfactant improves pulmonary function in endotoxin-induced lung injury. Am J Respir Crit Care Med 1998;158(3):840–845.
31. Anzueto A, Baughman RP, Guntupalli KK, Weg JG, Wiedemann HP, Raventos AA. Aerosolized surfactant in adults with sepsis-induced acute respiratory distress syndrome. Exosurf Acute Respiratory Distress Syndrome Study Group. N Engl J Med 1996;334(22): 1417–1421.
32. Dijk PH, Heikamp A, Oetomo SB. Surfactant nebulization versus instillation during high frequency ventilation in surfactant-deficient rabbits Pediatr Res 1998;44(5):699–704.
33. Oetomo SB, Dorrepaal C, Bos H, Gerritsen J, van der Mark TW, Koeter GH, van Aalderen WM. Surfactant nebulization does not alter airflow obstruction and bronchial responsiveness to histamine in asthmatic children. Am J Respir Crit Care Med 1996;153(3): 1148–1152.
34. Griese M, Bufler P, Teller J, Reinhardt D. Nebulization of the bovine surfactant in cystic fibrosis: a pilot study. European Respir J 1997; 10(9):1989–1994.
35. Anzueto A, Jubran A, Ohar JA, Piquette CA, Rennard SI, Colice G, et al. Effects of aerosolized surfactant in patients with stable chronic bronchitis: a prospective randomized controlled trial JAMA. 1997; 278(17):1426–1431.
36. MacIntyre NR, Baran G, Schuller F, Day S. A small diameter multilumen catherer for intraairway generation of therapeutic aerosols (abstract) Am J Respir Crit Care Med. 1996;153(4 Pt 2):A371.

Experimental Macromolecular Aerosol Therapy

Bruce K Rubin MEng MD

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Antiinflammatory Medications
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Rationale for Aerosol Mucoactive Therapy
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Growth Factors and Repair/Remodeling Factors
Anticancer Directed Targeting and Airway Immunization
Summary

[Respir Care 2000;45(6):684–694] *Key words: macromolecule, aerosol, mucoactive, mucolytic, gene transfer, mucociliary, clearance, cough, airway, inflammation.*

Introduction

The use of the inhalation route for the therapeutic administration of proteins and peptides dates back more than 70 years, when it was first shown that insulin could be absorbed from the lung following aerosol delivery.[1] The airway is an attractive target for the delivery of macromolecules, both for systemic administration and for the direct administration of therapeutic proteins and peptides to the airway surface. Until fairly recently, macromolecular delivery to the airway was limited by inefficient delivery systems, inexact dosing, impure peptides, and a paucity of macromolecular medications available for clinical use. This situation is rapidly changing, and an entire segment of the biotechnology industry is now focused on these applications. This article focuses on the promise of novel therapies based on the airway deposition of proteins, peptides, and other macromolecules.

To be effective, an aerosol medication must be stable in solution or suspension and stable to the shear forces associated with generation of the aerosol. The medication must efficiently deposit on the airway surface; for very expensive genetically engineered medications, deposition efficiency is critical. The medication must then penetrate into, and in some cases through, the mucus barrier to the appropriate target site of action (Fig. 1). For example, bronchodilators and glucocorticosteroids need to reach the ep-

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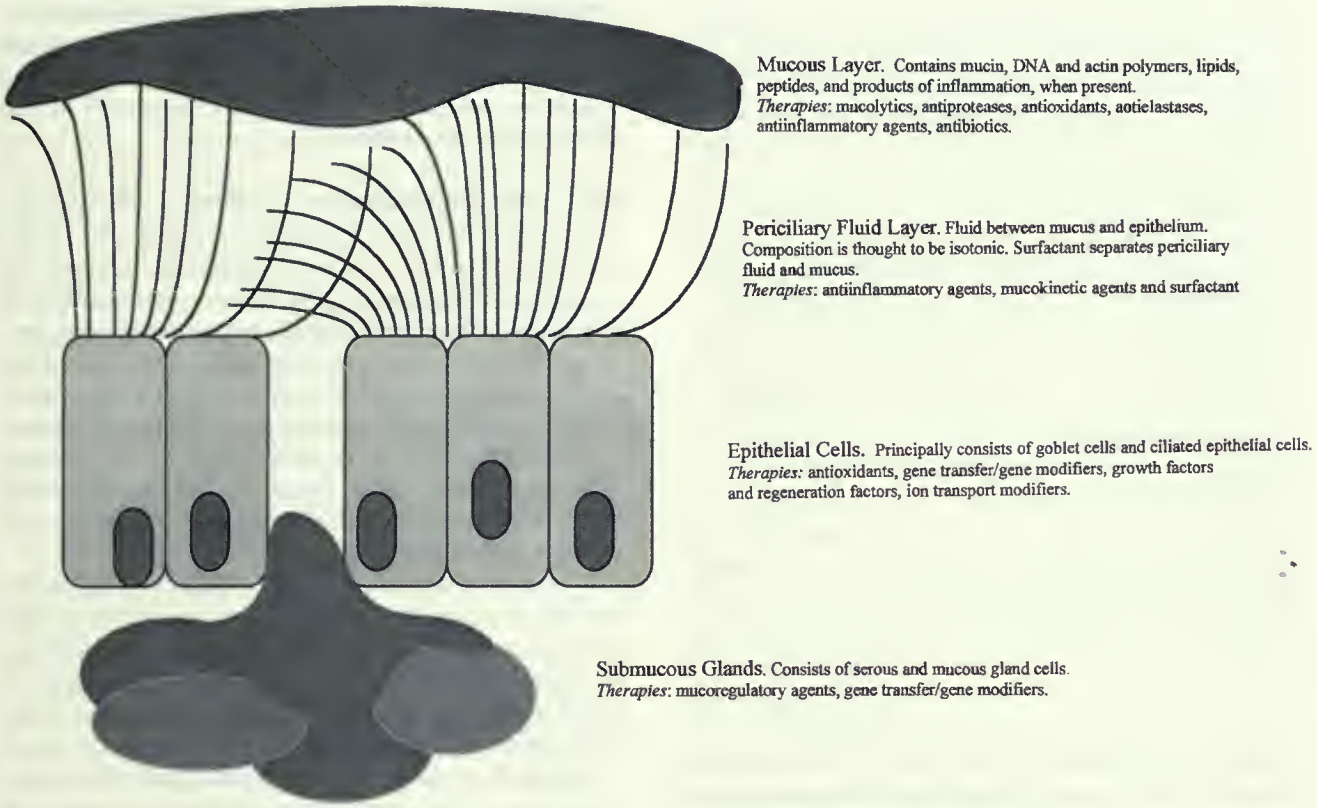
Mucous Layer. Contains mucin, DNA and actin polymers, lipids, peptides, and products of inflammation, when present.
Therapies: mucolytics, antiproteases, antioxidants, aotielastases, antiinflammatory agents, antibiotics.
Periciliary Fluid Layer. Fluid between mucus and epithelium. Composition is thought to be isotonic. Surfactant separates periciliary fluid and mucus.
Therapies: antiinflammatory agents, mucokinetic agents and surfactant
Epithelial Cells. Principally consists of goblet cells and ciliated epithelial cells.
Therapies: antioxidants, gene transfer/gene modifiers, growth factors and regeneration factors, ion transport modifiers.
Submucous Glands. Consists of serous and mucous gland cells.
Therapies: mucoregulatory agents, gene transfer/gene modifiers.

Fig. 1. Diagram of the airway epithelium, showing potential sites of drug targeting.

ithelium to be effective. Aerosolized antibiotics and mucolytics are most effective when dispersed in airway secretions at the sites of maximum airway obstruction. Gene transfer therapy must not only gain access to the epithelium through the mucus barrier but must then reach the submucous glands or the basal (progenitor) cells of the epithelium.

The mucous lining layer can be a substantial barrier to medications reaching the epithelium, especially when there is infection and inflammation. Particle charge, solubility and size, and the biophysical properties of mucus all affect the ability to penetrate the mucus barrier. There is a consistent inverse relationship between molecular weight and particle diffusion through mucus, most noted at molecular weights $>$ 30 kilodaltons (kDa).[2] Other factors limiting efficacy include binding to constituents of mucus, especially mucin and DNA, and to the breakdown of bioactive molecules by peptides and enzymes. Translocation of macromolecules can be further compromised by mucus hypersecretion that accompanies inflammation and chronic pulmonary disease.[3]

Factors promoting particle translocation through mucus include an effective surfactant layer and increased particle retention time. Mucus discontinuity in the airway can also promote deposition and translocation. In vitro experiments confirm that pulmonary surfactant promotes the displacement of some particles from air to the aqueous phase and that the extent of particle immersion depends on the surface tension of the surface active film. For particles $<$ 100 μm, the surface tension force is several orders of magnitude greater than forces related to gravity.[4] A surfactant vehicle has also been reported to increase the airway distribution of medications instilled intratracheally and can improve the uniformity of aerosol distribution.[5]

Antiinflammatory Medications

Pulmonary Inflammation

Inflammation is a response to a disruption of homeostasis, often by an exogenous insult. Pulmonary host defense can lead to an acute or chronic inflammatory response. Inflammation is associated with activation of inflammatory cells, including monocytes, neutrophils and eosinophils, generation of reactive oxygen and reactive nitrogen species, release of pro-inflammatory peptides and proteases, nervous system activation (neurogenic inflammation), and phospholipase activation (primarily sPLA2) with subsequent generation of kinins, leukotrienes, lyso-phospholipids, and other products of arachidonic acid metabolism (Table 1).

Table 1. Endogenous Mediators of Inflammation

Peptide mediators
Cytokines (IL-1, TNFα, IL-4 and IL-5, IL-6, IL-8)
Serine proteases (neutrophil elastase, neutral endopeptidase)
Adhesion molecules (ICAM, selectins)
Products of neurogenic inflammation
Nitric oxide
Peptide (NANC) mediators—VIP, substance-P
Lipid mediators—products of phospholipase activation
Lyso-phospholipids
Lipoxygenase metabolites of arachidonic acid—ecosinoids, leukotrienes
Cyclooxygenase metabolites of arachidonic acid—prostaglandins, thromboxane, kinins
Platelet activating factor
Reactive oxygen species (xanthine oxidase, myeloperoxidase)
Complement activation products

IL = interleukin. TNFα = tumor necrosis factor.
ICAM = intercellular adhesion molecule.
NANC = non-adrenergic non-cholinergic nervous system.
VIP = vasoactive intestinal polypeptide.

Inflammation also directly recruits neutrophils from the vascular space into the airway. This process is largely driven by the chemokine, interleukin 8. Neutrophils release myeloperoxidase, which uses hydrogen peroxide to generate reactive oxygen species. Neutrophils also release potent serine proteases such as neutrophil elastase that can lead to further tissue destruction and mucus hypersecretion, and cytokines that can exacerbate the inflammatory response in an autocrine mechanism recruiting and activating more neutrophils to the site of inflammation.[6] These self-perpetuating inflammation processes increase as a result of neutrophil necrosis. Neutrophil necrosis also spills nuclear DNA and filamentous actin (F-actin) into the airway, and these form elongated copolymers that contribute to the abnormal viscoelasticity and adhesiveness of sputum. Cystic fibrosis (CF), chronic obstructive pulmonary disease, bronchiectasis, and some forms of severe asthma are characterized by airway inflammation, with a predominantly neutrophil infiltration.

Rationale for Aerosol Antiinflammatory Therapy

Acute inflammation is essential for responding to environmental challenges or microorganisms, especially at epithelial surfaces. Acute inflammation is generally terminated by apoptosis (programmed cell death) of inflammatory cells. This process degrades intracellular DNA, proteases, and peptides, and allows for an orderly resolution of the inflammatory response. Chronic inflammation is induced, in part, by the persistence of the initiating factor and by host factors, and chronic inflammation is perpetuated by elements of the immune and inflammatory system, often released during inflammatory cell necrosis (disorderly death).

Therapeutic Approaches

Nonspecific Antiinflammatory Therapy. There is a tremendous amount of information related to the use of glucocorticosteroid aerosols as antiinflammatory agents, especially for the treatment of asthma. These data are reviewed elsewhere in this issue. Inhaled glucocorticoids also have the potential to down-regulate many components of the immune response, including production of inflammatory mediators, reactive oxygen species, and mucus hypersecretion. Many of these processes are driven by steroid-receptor-mediated inhibition of the nuclear transcription factor NFκB. There is active research into developing effective drugs to downregulate NFκB with tissue specificity.

Nonsteroidal antiinflammatory medications are antiinflammatory agents that primarily work by inhibition of the cyclooxygenase (COX) pathway of arachidonic acid metabolism (Table 2). Indomethacin, a COX-1 and COX-2 inhibitor, has been effectively administered via aerosol for the treatment of mucus hypersecretion associated with diffuse panbronchiolitis.[7] Although more specific COX-1 inhibitors have been developed, none have yet been tested as potential aerosol therapies.

Antiproteases. *Recombinant Secretory Leukoprotease Inhibitor.* Secretory leukoprotease inhibitor (SLPI), is a 12

Table 2. Antiinflammatory Agents

Nonspecific
Glucocorticosteroids
Antiproteases
Recombinant secretory leukoprotease inhibitor (rSLPI)
Alpha$_1$ antiprotease
Antineutrophil elastase
Antioxidants
Glutathione
Recombinant human superoxide dismutase (rSOD)
Cytokine modifiers
Anti IL-8
IL-4/5 r
Arachidonic acid metabolite modifiers
Nonsteroidal antiinflammatory agents (COX pathway)
Antisecretory phospholipases A_2
Antileukotriene agents (eg, LTD4 receptor antagonists)
COX-1 inhibitors
Platelet activating factor antagonists
Others
Phosphodiesterase inhibitors (PDE4-I)

IL = interleukin.

kDa serine antiprotease and the major inhibitor of neutrophil elastase on the epithelial surface of the upper airways.[8] When given to a small number of CF patients at a dose of 100 mg bid for 2 weeks, rSLPI decreased neutrophil elastase activity and interleukin 8 in airway surface fluid, but was ineffective at a dose of 50 mg bid. No important adverse effects were reported.[9] The half-life of rSLPI administered via aerosol in airway surface fluid was 12 hours. Following inhalation, rSLPI moves from the epithelium in an intact form into the interstitium of the lung.

Unexpectedly, aerosol administration of rSLPI to healthy sheep not only increased the antineutrophil elastase activity of the airway surface fluid, but also improved antioxidant protection by raising glutathione levels in the lung.[10] However, it may be more difficult to neutralize the burden of elastase in poorly ventilated, highly inflamed areas of the lung, as are seen in CF.[11]

rSLPI may also be active against mast cell and leukocyte serine proteases. The effects of rSLPI on antigen-induced pulmonary responses were evaluated in *Ascaris suum* sensitized sheep. Three milligrams rSLPI were administered via aerosol daily for 4 days, with the final dose given one-half hour before antigen challenge. This significantly reduced the areas under the curve for both early-phase and late-phase bronchoconstriction, by 73% and 95%, versus control. rSLPI also prevented antigen-induced decrease of tracheal mucus velocity.[12]

Alpha$_1$ proteinase inhibitor (α1PI). After aerosol administration of a single dose of 10–200 mg of recombinant α1PI, airway surface fluid antineutrophil elastase defenses were augmented in proportion to the dose of recombinant α1PI administered. Airway surface fluid α1PI levels and antineutrophil elastase capacity were increased by 40 times at 4 hours after the highest dose of recombinant α1PI, and were still increased 5 times over baseline 24 hours later.[13]

In a pilot clinical trial, α1PI was administered via aerosol to 12 clinically stable CF patients. After inhalation of the aerosol, neutrophil elastase activity was significantly decreased in airway surface fluid. α1PI also reversed the inhibitory effect of CF airway surface fluid on *Pseudomonas* killing by neutrophils in vitro.[14]

α1PI has also been administered to dogs via ultrasonic nebulizer. This produced particles with a mass median aerodynamic diameter (MMAD) small enough to allow them to reach the distal air spaces of the lung and that retained specific α1PI antineutrophil elastase activity.[15]

Interferon. Recombinant interferon gamma (rIFN-gamma) was administered via ultrasonic nebulization to mice that had been presensitized to ovalbumin (OVA). After repeated OVA aerosol administration over 10 days, the mice developed an asthma-like immunoglobulin E (IgE) response and airways hyperresponsiveness. Mice treated with rIFN-gamma via aerosol but not by the intraperitoneal route had a 66% decrease in serum anti-OVA IgE and a twofold increase in immunoglobin G2a levels. Cutaneous reactivity to OVA was reduced and airways hyperreactivity was also normalized after nebulized rIFN-gamma. However, the treatment had to begin before day 7 of OVA exposure in order to decrease anti-OVA IgE, and only treatment regimens that included 3 days of nebulized IFN-gamma *before* OVA sensitization caused a decrease in cutaneous reactivity and normalization of airway responsiveness.[16] Recombinant IFN-gamma has also been safely administered via aerosol to healthy people in a pilot trial.[17]

Interferon-alpha (IFN-alpha) has antimicrobial activity against many intracellular bacteria, including *Mycobacterium tuberculosis*. Aerosolized IFN-alpha (3 μg/dose) was given 3 times a week to patients with documented active pulmonary tuberculosis. Two groups of 10 patients each were evaluated before and after 2 months of conventional antituberculous chemotherapy with or without inhaled IFN-alpha. Fever, *Mycobacterium* sputum density, and abnormalities in high-resolution computed tomography images all showed significantly earlier resolution in the IFN-alpha-treated group.[18]

Antioxidants. In inflammatory lung disorders, oxidants and proteases are synergistic in their potential to destroy lung parenchyma. In the healthy lung, the oxidant burden is balanced by local antioxidant defenses. However, an increased oxidant burden and/or decreased antioxidant defenses can reverse the oxidant-antioxidant balance, leading to lung injury. Macrophages in the airways and the alveolar spaces can release reactive oxygen and reactive nitrogen species after phagocytosis of inhaled particles. As a result, signal transduction pathways are set in motion that contribute to inflammation in the airway. These effects include increased expression of intercellular adhesion molecule 1, interleukin 6, cytosolic and inducible nitric oxide synthase, manganese superoxide dismutase (SOD), phospholipase A_2, and mucus hypersecretion.

Reduced glutathione. Glutathione plays an important role in the endogenous antioxidant defense system, and plasma oxidized glutathione level is as a sensitive indicator of in vivo oxidant stress. Studies using reduced glutathione as a therapeutic agent found that reduced glutathione can be administered directly to the respiratory epithelial surface by aerosol and is fully functional as an antioxidant, both in vitro and in vivo.[19]

Superoxide dismutase. Recombinant human Cu^{++}/Zn^{++} superoxide dismutase (rSOD), a major pulmonary antioxidant, was aerosolized to sheep and the levels of human SOD and antisuperoxide anion capacity were quantified in airway surface fluid over time. rSOD-specific activity was retained after nebulization, and there was a substantial increase in both the amount of SOD and the antisuperox-

ide anion capacity that persisted for several hours after administration.[20]

Antioxidant vitamins. Aerosol particles of vitamin E, an antioxidant vitamin, were formed by rapid expansion of supercritical CO_2. These were administered to rats, increasing pulmonary vitamin E levels and decreasing neutrophil-mediated lung vascular leak. Pretreatment with supercritical-CO_2-formed aerosol vitamin E protected isolated rat lungs against the oxidant-induced lung leak caused by perfusion with xanthine oxidase and purine, an enzyme system that generates superoxide anion and hydrogen peroxide.[21]

Mucoactive Medications

In health, airway surface fluid is a bilayer, with periciliary fluid interposed between the epithelium and the mucous gel. The mucous gel and periciliary fluid are separated by a thin layer of surfactant.[22] The mucous layer is thought to be 2–10 μm thick in the trachea, and extends from the bronchioles to the upper airway. This layer becomes discontinuous in the bronchioles, and some investigators have suggested that the mucous layer is discontinuous even in large airways, except under conditions of stimulated secretion. Mucus is an inhomogeneous, viscoelastic, adhesive gel containing water, sugars, proteins, and lipids. It is a normal product of mucous (goblet) cells and mucous glands. Mucus is transported from the lower respiratory tract into the pharynx by ciliary clearance. Sputum consists of lower respiratory tract secretions and debris, including microorganisms, cells, and neutrophil-derived DNA and F-actin polymers. Sputum is primarily cleared by air flow.

Rationale for Aerosol Mucoactive Therapy

There are several mechanisms whereby mucoactive medications could improve the mobilization of secretions (mucokinesis) or reduce the volume of secretions in the airway (mucoregulation). These mechanisms include reducing airway inflammation, increasing ciliary beat frequency or power, decreasing sputum adhesion to the epithelium, increasing air flow, and changing the biophysical properties of the secretions. We base the classification of mucoactive agents on the primary mechanism whereby each is thought to promote mucus clearance.[23] *Mucoactive therapy* is the general term that we use for all medications that affect mucus properties or mucus clearance.

Mucoactive Medications

Expectorants are meant to increase the volume or hydration of airway secretions. Systemic hydration and classic expectorants (guaifenesin, iodide) have not been found to be clinically effective. Modifiers of airway water transport, including tricyclic nucleotides (through the purinergic P2Y pathway) and gene transfer therapy are under investigation.

Mucolytics degrade polymers in secretions (Table 3). The classic mucolytics have free thiol groups that degrade mucin, and peptide mucolytics break pathologic filaments of neutrophil-derived DNA and F-actin. Low-molecular-weight saccharide compounds can disrupt the tangled mucin polymer network, primarily through ionic interactions. These agents appear to be effective in some chronic inflammatory airway diseases.

Mucokinetics increase cough efficiency. Cough flow can be increased by bronchodilators in patients with airway hyperreactivity. Abhesives, especially surfactants, decrease epithelial-mucus attachment, augmenting both cough and mucociliary clearance.

Mucoregulatory agents reduce the volume of airway mucus and appear to be especially effective in hypersecretory states like bronchorrhea, diffuse panbronchiolitis, and some forms of asthma. These medications include antiinflammatory agents, anticholinergic agents, and some macrolide antibiotics.

Therapeutic Approaches - Mucolytics

The physical characterization of secretions includes both bulk physical (rheologic) and surface properties. Rheology (viscoelasticity) measurements describe how a material responds to an applied stress. Mucus is a viscoelastic or non-Newtonian fluid because it has both liquid-like (viscous) and solid-like (elastic) properties. *Viscosity* is the resistance to flow, and represents the capacity of a material to absorb and dissipate applied energy (stress). *Elasticity* is the capacity of a material to store applied energy. An ideal, or Hookian, solid responds to a stress with a finite deformation (strain), which is recovered after the stress is removed. An ideal liquid responds to a stress by flowing

Table 3. Mucoactive Agents

Mucolytics
Classic mucolytics—degrade mucin polymers
Peptide mucolytics—degrade DNA and F-actin polymers
Low molecular weight saccharide compounds
Mucokinetics
Surfactants
Bronchodilators
Ciliary stimulators
Mucoregulatory agents
Anticholinergics
Macrolide antibiotics
Indomethacin
Glucocorticosteroids

during the time that the stress is applied. After removing the stress, flow ceases and there is no recovery of energy. Mucus responds to stress with an initial elastic storage of energy, followed by a viscoelastic deformation, and finally by a period of liquid-like steady flow in which the rate of deformation is fairly constant.[24] The secretion and transport of mucus require that mucus exhibit this non-Newtonian behavior. If mucus were an ideal solid, it could not be extruded from the glands, and if it were an ideal liquid, there could be no efficient transfer of energy from beating cilia. Mucus with too great a viscosity or elasticity, or too low an elasticity, is poorly transported by cilia.[25–27]

Mucolytic medications reduce viscosity by disrupting polymer networks in the secretions. Classic mucolytic agents work by severing disulfide bonds, binding calcium, depolymerizing mucopolysaccharides, and liquefying proteins. Saccharide mucolytics dissociate the mucin entanglements without depolymerizing the mucin filaments. Peptide mucolytics degrade pathologic filaments of DNA and F-actin.

As requested by the organizers of the consensus conference, the discussion here is limited to mucolytic agents. Expectorant, mucokinetic, and mucoregulatory agents can also be delivered via aerosol. These are discussed elsewhere.[23]

Classic Mucolytics. Classic mucolytic medications disrupt mucin glycoproteins. Agents containing free sulfhydryl groups reduce the disulfide bridges crosslinking mucin molecules. N-acetyl L-cysteine (NAC) is a general example of this class of drugs. Evidence for the efficacy of NAC is weak,[28,29] and inhaled NAC can cause bronchospasm and airway inflammation.[30] There are no data that clearly support the use of this or similar agents as mucolytics.

Nacystelyn (N-acetylcysteine lysinate) is a newer agent, which combines NAC with the basic amino acid lysine. This agent is more pH-neutral than NAC (pH 6.2 vs 2.2), potentially reducing the risk of airway inflammation after aerosol administration. In experiments comparing the effects of NAC and nacystelyn administered via aerosol to healthy anaesthetized dogs, nacystelyn also appeared to have greater mucolytic activity than NAC.[31]

Low-Molecular-Weight Saccharide Compounds. Mucins are glycoconjugates in which carbohydrate side chains are linked to a protein backbone by O-glycosidic bonds between N-acetylgalactosamine and serine or threonine. The individual glycoprotein chains are held together by low-energy noncovalent bonds, including ionic, hydrogen, and van der Waal forces, thus forming a tangled network. Saccharide compounds can osmotically draw fluid into the airway, increasing mucus hydration and mucociliary clearance. Saccharides may also dissociate mucin polymers by affecting ionic charge interactions and hydrogen bonds, reducing mucin crosslink density without reducing polymer length. This mechanism is probably optimal for saccharide units that match the length of mucin oligosaccharides.[32]

Peptide Mucolytics. Sputum contains products of inflammation, including neutrophil-derived DNA and F-actin that greatly contribute to the rheologic properties of sputum. High-molecular-weight DNA is present in CF sputum in concentrations $\geq$ 15 mg/mL. DNA and F-actin copolymerize to form a rigid network entangled with the mucin gel.[33] Peptide mucolytics degrade these abnormal filaments.

Recombinant Human DNase I. Recombinant human DNase I (dornase alfa) was the first mucolytic agent approved in the United States for the treatment of CF lung disease.[34] In the pivotal multicenter study, 320 patients with stable CF lung disease and a forced vital capacity of $< 40\%$ predicted were given an aerosol of either 2.5 mg dornase alfa once daily or excipient for 12 weeks. Patients receiving dornase alfa had a 12.4% improvement in forced expiratory volume in the first second (FEV_1) above baseline, compared with a 2.1% increase in those receiving placebo. Therapy was safe and well tolerated but dyspnea was more common in the dornase alfa group, and the presence of dyspnea was associated with a decreased response.[35] Dornase alfa aerosol has not been found to be effective for the therapy of other airway diseases, such as chronic bronchitis or bronchiectasis. In fact, pulmonary exacerbations were more frequent and FEV_1 decline was greater in patients who received recombinant human DNase than in those who received placebo, during a 24-week clinical trial in patients with clinically stable bronchiectasis.[36]

As part of the evaluation of dornase alfa for clinical use, several nebulizer systems were tested. The Hudson Updraft T and the Acorn II, both driven by Pulmo-Aide compressors, were both compared to the Pari LC driven by a Pari compressor. All 3 nebulizers were equivalent with regard to particle size (MMAD), total dose nebulized, and the fine particle fraction delivered.[37]

The effect of droplet size on safety and efficacy was investigated in two further studies. The Hudson Up-draft T nebulizer driven by a Pulmo-Aide compressor was compared to the reusable Medicaid Sidestream nebulizer driven by a CR50 compressor. These systems deliver aerosols with MMADs of 3.5 μm and 5 μm, respectively. Although no statistical difference was observed in this small study (suggesting a Type II error), there was a trend toward a greater response for the smaller MMAD aerosol (Hudson Up-draft T), as measured by forced vital capacity and FEV_1.[38] Similarly, the Hudson Up-draft T driven by a

Pulmo-Aide compressor was again compared to the Medicaid Sidestream nebulizer, this time driven by a MobileAire compressor. Again there was again a trend to a greater response with the smaller aerosol droplets generated by the Hudson Up-draft T.[39]

Note that not all nebulizers that provide similar droplet size can be used with dornase alfa. In particular, the heat of ultrasonic devices can denature the dornase alfa, causing protein aggregation and loss of activity.[40]

Actin Depolymerizing Agents. Actin is the most prevalent cellular protein in the body, and it plays a vital role in maintaining the structural integrity of cells. Under certain conditions, actin polymerizes to form filamentous or F-actin. By co-polymerizing with DNA (separate from the mucin polymer network) extracellular F-actin can contribute to the viscoelasticity of sputum. F-actin concentrations in CF sputum have been reported to be as great as 0.15 mg/mL, and there is an increased ratio of F-actin to G-actin in CF sputum, compared to normal secretions. Gelsolin is an 85 kDa (577 residue) actin-severing peptide that can reduce the viscosity of CF sputum in vitro.[41] The large size of this peptide makes it somewhat difficult to manufacture and to efficiently nebulize.

Thymosin $\beta 4$ is the principal actin-sequestering peptide in humans. This small (4.8 kDa) and very soluble peptide is less than one sixth the size of recombinant human DNase and one twentieth the size of gelsolin. By sequestering G-actin, thymosin $\beta 4$ promotes the depolymerization of F-actin and inhibits the formation of actin filaments. Thymosin $\beta 4$ has also been shown to efficiently decrease the viscosity of CF sputum in vitro.[42]

Therapeutic Outcomes Assessment

Patients most likely to benefit from mucoactive therapy usually have a history of increased sputum expectoration and fairly well preserved expiratory air flow (FEV_1 > 30% of predicted). With the exception of external chest wall oscillation, most clearance-assist devices and mucoactive medications are less beneficial in patients with very severe lung disease. Theoretically, when air flow is profoundly compromised, mucolytic agents could reduce sputum clearance because of retrograde flow of airway secretions.

The effectiveness of therapy in an individual patient can be difficult to assess. When the patient feels better and there is an improvement in air flow and/or a reduction in trapped thoracic gas, benefit is clear. However, changes in FEV_1 poorly reflect clinical improvement with mucoactive therapy. Intuitively, one might expect that expectorated sputum volume would be a good way to assess the effectiveness of therapy, but changes in expectorated sputum volume relate poorly to changes in pulmonary function or the clinical status of the patient. This is partly because of limitations of measuring sputum volume, because of patient reluctance to expectorate, swallowing of secretions, and salivary contamination of secretions. The sputum volume is variable from day to day and at different times of the day. Finally, an increased volume of collected secretions could represent either increased mucus clearance or increased mucus production.[43]

Patients with acute mucus retention (eg, acute bronchitis or exacerbations of CF lung disease) may be less responsive to mucoactive medications than stable patients. This may be due to decreased air flow caused both by the increase in infection and by muscular weakness further reducing air flow-dependent clearance mechanisms.[44]

Gene Transfer

Rationale: The Genetic Basis for Airway Disease

Theoretically, the ultimate therapy would be to safely and permanently correct the basic genetic defect in persons with diseases such as CF. Indeed, most of the research to date has been on developing gene therapy for CF. However, data are accumulating that suggest a genetic basis for some, if not most, forms of asthma. There also appears to be both a genetic basis for susceptibility to chronic obstructive pulmonary disease and resistance to chronic obstructive pulmonary disease in some very heavy smokers. For example, patients with a deficiency of effective $alpha_1$ protease inhibitor are at far greater risk of developing emphysema and at a much younger age than smokers who do not have this genetic mutation. Gene therapy could potentially be used to inactivate susceptibility genes or even oncogenes (genes that can induce cancer, generally by preventing cell death). Gene therapy might also be used to introduce a "resistance" or "repair" gene into the airway of otherwise susceptible individuals.

Difficulties with gene transfer at this time include targeting the appropriate cell(s) for therapy, the stability of the gene complementation, including the longevity of the transfected airway cells, helping the vector to evade local and systemic immune responses, and successful activation of the new gene after transfer (Table 4).

Virus Vectors

Replication Defective Adenovirus Vector. CF gene therapy was first attempted by inserting the normal cystic fibrosis transmembrane conductance regulator protein (CFTR) gene into a replication defective adenovirus (RD-adenovirus) vector. Cells were transfected by the RD-adenovirus vector in vitro and produced small amounts of normal CFTR.[45] However, in the initial human trials, an RD-adenovirus induced a substantial inflammatory re-

Table 4. Gene Transfer Vectors

Viruses
Adenovirus
Lentivirus
Adeno-associated virus (AAV)
Non-virus
Naked DNA
Liposome-mediated transfer

sponse that limited the usefulness of the vector. As well, the host humoral immune response to the genetically modified cells generated neutralizing antibodies that increased the risk of readministering the vector. If the RD-adenovirus vector could be made less immunogenic, it would be safer and have more stable expression once in the cell.

RD-adenovirus carrying the CFTR gene has been effectively delivered via aerosol to the airways of nonhuman primates, with gene transfer documented and minimal adverse effects noted.[46,47] Initial trials of aerosol delivery of RD-adenovirus carrying the CFTR gene to humans with CF have shown similar results.[48]

Adeno-Associated Virus. Adeno-associated Virus (AAV) is a small single-stranded DNA parvovirus that is naturally replication defective and not pathogenic. When AAV infects a cell, it usually requires co-infection with a helper virus to replicate and propagate. Infected with wild type AAV alone, the virus tends to become latent by stably integrating into a specific area on chromosome 19, minimizing the risk of insertional mutagenesis (ie, inadvertent activation of oncogenes). The AAV has a small package capacity with not much room for both CFTR cDNA and regulatory elements. This is very important not only for producing the vectors, but also because AAV *rep* gene products are needed for site-specific integration, meaning that AAV vectors without these regulatory elements can integrate at multiple sites and may not integrate at all unless the cell divides. Early trials suggest that the CFTR gene package can be transferred successfully with safe and stable vector expression.[49]

Lentiviruses. Both the adenovirus and the AAV infect or transfect terminally differentiated cells, meaning that at this time the CFTR cDNA can only be targeted to nondividing cells rather than to progenitor or stem cells. Once the transfected cells naturally die and are shed, the cells taking their place in the epithelium will not carry the cDNA package, and so repeat administration of the vector is needed. The airway epithelial cells turn over in about 60 days in healthy individuals and in a much shorter time in the infected and inflamed airway.

Lentiviruses are retroviruses (such as the human immunodeficiency virus) with the ability to integrate into chromosomal DNA, with stable and long-lasting expression that is passed on to daughter cells. Because the integration site is random, there is the possibility of insertional mutagenesis, and this risk increases as a greater number of cells are infected. Although some lentiviruses are unable to infect post-mitotic cells, others, including the human immunodeficiency virus, do not require cell division to insert their genome.[50]

Non-Virus Vectors

Naked cDNA can transfect target cells in culture, but the efficiency of transfection is so low as to preclude this as an effective means of gene transfer. However, by complexing the cDNA with lipophilic carriers such as lectins or liposomes, it is possible to increase the transfection efficiency to make effective gene transfer a possibility.

Cationic liposomes are lipid capsules that can form complexes with DNA, attach to the lipid-bilayer cell membrane, and then enter cells. With the first generation of liposome vectors, the efficiency of gene transfer was poor, but this has improved dramatically with newer systems. Nevertheless, transfer of DNA from the liposome into the cell nucleus is still relatively inefficient. Although most cationic lipids are toxic to cultured cells and can cause inflammation in animal systems, pilot studies have shown no important cellular damage after exposure to liposome vectors.[51] The duration of gene expression after liposome-mediated gene transfer has been transient, making frequent administration likely to be necessary. Aerosol delivery of transgenes using cationic lipids is also limited by the ability to generate highly concentrated formulations of lipid—DNA complexes that are stable and retain activity following aerosolization.[52,53]

Gene transfer to airway cells is impaired by the addition of a mucus layer in vitro. Treatment of CF-sputum-covered cell lines with dornase alfa at a dose of 50 μg/mL significantly improved liposomal gene transfer. On the other hand, treatment of the cell lines with NAC, nacystelyn, lysine, or recombinant alginase was ineffective at enhancing gene transfer.[54]

Looking to the Future

As the ability to identify, purify, synthesize, and solubilize or suspend peptides and other macromolecules for aerosol delivery improves in efficiency and economy, we will see the introduction of a number of novel therapeutic agents. The lung is a superb potential target for drug delivery because of relatively easy accessibility, the large absorptive surface area, the unique resident immune cells, and the physiology of the pulmonary and bronchial circulation.

Specific MUC Gene Therapy

The protein backbones of mucins are encoded by MUC genes. Of the 9 human MUC genes identified to date, seven are expressed in the respiratory tract. MUC5/5AC and MUC4 are generally localized to goblet cells, while MUC5B, MUC8, and MUC7 localize to submucosal glandular cells. MUC5/5AC is the predominant mucin mRNA expressed in the airway, and there is increased airway MUC2 expression induced by inflammation. Because mature mucins are heavily glycosylated, it is has been difficult to raise antibodies specific for naked protein stretches of specific MUC mucins, which would enable us to associate increased MUC mRNA with increased MUC protein.[55] As these antibodies become available, we may find that increases in specific MUC mucins may be fairly specific markers that identify the nature of airway injury, and these may be targets for specific mucolytic or mucoregulatory therapy.

Gene Modulation and "Gene Repair"

The difficulties associated with current vector systems for efficient and stable CFTR gene transfer have led to the development of a number of medications designed for CFTR gene modulation or "gene repair." Although at this time (late 1999) over 700 CFTR gene defects have been identified, a 3-base deletion removing a phenylaline residue at position 508 of CFTR (the ΔF508 mutation) is the most commonly found in the white population, and this deletion is found on approximately 70% of CF chromosomes. Thus, most of the effort to date has been directed toward activating this specific CF gene mutation.

For the CFTR protein to function as a chloride channel, it must first be properly assembled and glycosylated, and then must be transported intact and inserted into the cell membrane. Improperly assembled CFTR can be degraded before it reaches the cell membrane. Because the ΔF508 mutation retains some channel function once inserted into the cell membrane, there is great interest in finding ways to get more mutant ΔF508 protein glycosylated and out to the cell surface. A variety of agents, including the xanthine A1 adenosine receptor antagonist CPX (8-cyclopentyl-1, 3-dipropylxanthine), the tyrosine kinase inhibitor genistein, the transcription regulator phenylbutyrate (sodium 4-phenylbutyric acid), the type III phosphodiesterase inhibitors, the activators of G proteins (milrinone and amrinone), and some chemical chaperones that may prevent degradation of the ΔF508 CFTR protein have all shown promise in either activating ΔF508 CFTR or preventing its degradation in the Golgi apparatus.[56] Most of these have only been studied in vitro, but aerosol administration of these relatively small molecules holds great promise. Similar gene modifiers may be of value for other acute and chronic airway diseases.

Growth Factors and Repair/Remodeling Factors

Chronic airway disease can lead to fibrosis and airway destruction (emphysema and bronchiectasis). This is balanced by airway repair and regeneration that are regulated by interactions between the injured epithelium and growth factors, including cytokines and chemokines, and matrix metalloproteinases. It is likely that some of these growth and repair factors could be administered to the injured airway, promoting normal healing and inhibiting the development of pulmonary fibrosis. Before this becomes a reality, these peptides will need to be identified, purified, efficiently produced, and tested first for safety (eg, to be certain that they do not promote unimpeded epithelial growth) and then for efficacy.

Anticancer Directed Targeting and Airway Immunization

The airway is a unique immune milieu, constantly sampling the environment with the inhaled air and reacting to foreign material and microorganisms. This makes the airway an attractive target for immunization and immunomodulation, not only for respiratory pathogens, but potentially for systemic immunization against pathogenic microorganisms and perhaps for metaplastic and cancerous cells as well.

It may also be possible to treat some forms of lung cancer by the administration of aerosolized antineoplastic agents directly targeting the tumor and metaplastic epithelium. Because of the tremendous systemic toxicity associated with anticancer agents, this has the potential to decrease both medication toxicity and costs. Furthermore, the inhalation route may be much more attractive to patients and caregivers than long-term intravenous access used to administer therapy.

Summary

These novel and experimental therapies have the potential of drastically altering our understanding of and approach to airway disease. We indeed live in interesting times.

REFERENCES

1. Gaensslen M. Über inhalation von Insulin. Wein Klin. Wochenschr. 1925;2:71–72.
2. Desai MA, Mutlu M, Vadgama P. A study of macromolecular diffusion through native porcine mucus. Experientia 1992;48(1):22–26.

3. Bhat PG, Flanagan DR, Donovan MD. Drug diffusion through cystic fibrotic mucus: steady-state permeation, rheologic properties, and glycoprotein morphology. J Pharm Sci 1996;85(6):624–630.
4. Schürch S, Gehr P, Im Hof V, Geiser M, Green F. Surfactant displaces particles toward the epithelium in airways and alveoli. Respir Physiol 1990;80(1):17–32.
5. Kharasch VS, Sweeney TD, Fredberg J, Lehr J, Damokosh AI, Avery ME, Brain JD. Pulmonary surfactant as a vehicle for intratracheal delivery of technetium sulfur colloid and pentamidine in hamster lungs. Am Rev Respir Dis 1991;144(4):909–913.
6. Adler KB, Fischer BM, Wright DT, Cohn LA, Becker S. Interactions between respiratory epithelial cells and cytokines: relationships to lung inflammation (review). Ann NY Acad Sci 1994;725:128–145.
7. Tamaoki J, Chiyotani A, Kobayashi K, Sakai N, Kanemura T, Takizawa T. Effect of indomethacin on bronchorrhea in patients with chronic bronchitis, diffuse panbronchiolitis, or bronchiectasis. Am Rev Respir Dis 1992;145(3):548–552.
8. Vogelmeier C, Gillissen A, Buhl R. Use of secretory leukoprotease inhibitor to augment lung antineutrophil elastase activity (review). Chest 1996;110 (6 Suppl):261S–266S.
9. McElvaney NG, Nakamura H, Birrer P, Hebert CA, Wong WL, Alphonso M, et al. Modulation of airway inflammation in cystic fibrosis: in vivo suppression of interleukin-8 levels on the respiratory epithelial surface by aerosolization of recombinant secretory leukoprotease inhibitor. J Clin Invest 1992;90(4):1296–1301.
10. Gillissen A, Birrer P, McElvaney NG, Buhl R, Vogelmeier C, Hoyt RF Jr, et al. Recombinant secretory leukoprotease inhibitor augments glutathione levels in lung epithelial lining fluid. J Applied Physiol 1993;75(2):825–32.
11. Stolk J, Camps J, Feitsma HI, Hermans J, Dijkman JH, Pauwels EK. Pulmonary deposition and disappearance of aerosolised secretory leucocyte protease inhibitor. Thorax 1995;50(6):645–50.
12. Wright CD, Havill AM, Middleton SC, Kashem MA, Lee PA, Dripps DJ, et al. Secretory leukocyte protease inhibitor prevents allergen-induced pulmonary responses in animal models of asthma. J Pharmacol Exp Ther 1999;289(2):1007–1014.
13. Hubbard RC, McElvaney NG, Sellers SE, Healy JT, Czerski DB, Crystal RG. Recombinant DNA-produced alpha 1-antitrypsin administered by aerosol augments lower respiratory tract anti-neutrophil elastase defenses in individuals with alpha 1-antitrypsin deficiency. J Clin Invest 1989;84(4):1349–1354.
14. McElvaney NG, Hubbard RC, Birrer P, Chernick MS, Caplan DB, Frank MM, Crystal RG. Aerosol alpha 1-antitrypsin treatment for cystic fibrosis. Lancet 1991;337(8738):392–394.
15. Smith RM, Spragg RG. Production and administration to dogs of aerosols of alpha-1-proteinase inhibitor. Am J Med 1988;84(6A): 48–51.
16. Lack G, Renz H, Saloga J, Bradley KL, Loader J, Leung DY, et al. Nebulized but not parenteral IFN-gamma decreases IgE production and normalizes airways function in a murine model of allergen sensitization. J Immunol 1994;152(5):2546–2554.
17. Martin RJ, Boguniewicz M, Henson JE, Oelniker AC, Williams M, Giorno RC, Leung DY. The effects of inhaled interferon gamma in normal human airways. Am Rev Respir Dis 1993;148(6 Pt 1):1677–1682.
18. Giosue S, Casarini M, Alemanno L, Galluccio G, Mattia P, Pedicelli G, et al. Effects of aerosolized interferon-alpha in patients with pulmonary tuberculosis. Am J Respir Crit Care Med 1998;158(4):1156–1162.
19. Buhl R, Meyer A, Vogelmeier C. Oxidant-protease interaction in the lung: prospects for antioxidant therapy (review). Chest 1996;110 (6 Suppl):267S–272S.
20. Gillissen A, Roum JH, Hoyt RF, Crystal RG. Aerosolization of superoxide dismutase: augmentation of respiratory epithelial lining fluid antioxidant screen by aerosolization of recombinant human Cu + + /Zn + + superoxide dismutase. Chest 1993;104(3):811–815.
21. Hybertson BM, Kitlowski RP, Jepson EK, Repine JE. Supercritical fluid-aerosolized vitamin E pretreatment decreases leak in isolated oxidant-perfused rat lungs. J Appl Physiol 1998;84(1):263–268.
22. Morgenroth K, Bolz J. Morphological features of the interaction between mucus and surfactant on the bronchial mucosa. Respiration 1985;47(3):225–231.
23. Rubin BK, Tomkiewicz RP, King M. Mucoactive agents: old and new. In: Wilmott RW, editor. The pediatric lung. Basel, Switzerland: Birkhäuser Publishing; 1997: 155–179.
24. King M, Rubin BK. Mucus rheology: relationship with transport.In: Takishima T, editor. Airway secretion: physiological bases for the control of mucus hypersecretion. New York: Marcel Dekker; 1994: 283–314.
25. King M, Rubin BK. Mucus physiology and pathophysiology: therapeutic aspects. In: Derenne JP, Similowski T, Whitelaw WA, editors. Chronic obstructive lung disease. New York: Marcel Dekker; 1996: 391–411.
26. Puchelle E, Zahm JM, Girard F, Bertrand A, Polu JM, Aug F, Sadoul P. Mucociliary transport in vivo and in vitro: relations to sputum properties in chronic bronchitis. Eur J Respir Dis 1980;61(5):254–264.
27. Rubin BK, MacLeod PM, Sturgess J, King M. Recurrent respiratory infections in a child with fucosidosis: is the mucus too thin for effective transport? Pediatr Pulmonol 1991;10(4):304–309.
28. Ducholm M, Nielsen C, Thorshauge H, Evald T, Hansen NC, Madsen HD, Maltbaek N. N-acetylcysteine by metered dose inhaler in the treatment of chronic bronchitis: a multi-centre study. Respir Med 1992;86(2):89–92.
29. Hansen NCG, Skriver A, Brorsen-Riis L, Balslov S, Evald T, Maltbaek N, et al. Orally administered N-acetylcysteine may improve general well-being in patients with mild chronic bronchitis. Respir Med 1994;88(7):531–535.
30. Ventresca GP, Cicchetti, Ferrari V. Acetylcysteine. In: Braga PC, Allegra L, editors. Drugs in bronchial mucology. New York: Raven Press; 1989: 77–102.
31. Tomkiewicz RP, App EM, De Sanctis GT, Coffiner M, Maes P, Rubin BK, King M. A comparison of a new mucolytic N-acetylcysteine L-lysinate with N-acetylcysteine: airway epithelial function and mucus changes in dog. Pulm Pharmacol 1995;8(6):259–265.
32. Feng W, Garrett H, Speert DP, King M. Improved clearability of cystic fibrosis sputum with dextran treatment in vitro. Am J Respir Crit Care Med 1998;157(3 Pt 1):710–714.
33. Tomkiewicz RP, Kishioka C, Freeman J, Rubin BK. DNA and actin filament ultrastructure in cystic fibrosis sputum. In: Baum G. Cilia, mucus, and mucociliary interactions. New York: Marcel Dekker; 1998: 333–341.
34. Shak S. Aerosolized recombinant human DNase I for the treatment of cystic fibrosis (review). Chest 1995;107(2 Suppl):65S–70S.
35. Fuchs HJ, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Ramsey BW, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. N Engl J Med 1994;331(10):637–642.
36. O'Donnell AE, Barker AF, Ilowite JS, Fick RB. Treatment of idiopathic bronchiectasis with aerosolized recombinant human DNase I. rhDNase Study Group. Chest 1998;113(5):1329–1334.
37. Fiel SB, Fuchs HJ, Johnson C, Gonda I, Clark AR. Comparison of three jet nebulizer aerosol delivery systems used to administer re-

combinant human DNase I to patients with cystic fibrosis. The Pulmozyme rhDNase Study Group. Chest 1995;108(1):153–156.
38. Shah PL, Scott SF, Geddes DM, Hodson ME. Two years experience with recombinant human DNase I in the treatment of pulmonary disease in cystic fibrosis. Respir Med 1995;89(7):499–502.
39. Geller DE, Eigen H, Fiel SB, Clark A, Lamarre AP, Johnson CA, Konstan MW. Effect of smaller droplet size of dornase alfa on lung function in mild cystic fibrosis. Dornase Alfa Nebulizer Group. Pediatr Pulmonol 1998;25(2):83–87.
40. Cipolla DC, Clark AR, Chan H-K, Gonja I, Shire S J. Assessment of aerosol delivery systems for recombinant human deoxyribonuclease: STP Pharma Sci 1994;4:50–62.
41. Vasconcellos CA, Allen PG, Wohl ME, Drazen JM, Janmey PA, Stossel TP. Reduction in viscosity of cystic fibrosis sputum in vitro by gelsolin. Science 1994;263(5149):969–971.
42. Rubin BK, Kater AP, Dian T, Ramirez OE, Tomkiewicz RP, Goldstein AL. Effects of thymosin beta 4 on cystic fibrosis sputum. Pediatr Pulmonol Suppl 1995;12:234.
43. Rubin BK. Pharmacologic management of mucus retention based on a taxonomy of mucoactive medications. In: Baum G. Cilia, mucus, and mucociliary interactions. New York: Marcel Dekker; 1988: 383–389.
44. Rubin BK, Kishioka C, van der Schans CP, Dowell A, Fiel S. Mucus and mucoactive therapy in chronic bronchitis. Clin Pulm Med 1998; 5:1–14.
45. Knowles MR, Hohneker KW, Zhou Z, Olsen JC, Noah TL, Hu PC, et al. A controlled study of adenoviral-vector-mediated gene transfer in the nasal epithelium of patients with cystic fobrosis. N Engl J Med 1995:333(13):823–831.
46. McDonald RJ, Lukason MJ, Raabe OG, Canfield DR, Burr EA, Kaplan JM, et al. Safety of airway gene transfer with Ad2/CFTR2: aerosol administration in the nonhuman primate. Hum Gene Ther 1997;8(4):411–422.
47. Sene C, Bout A, Imler JL, Schultz H, Willemot JM, Hennebel V, et al. Aerosol-mediated delivery of recombinant adenovirus to the airways of nonhuman primates. Hum Gene Ther 1995;6(12):1587–1593.
48. Bellon G, Michel-Calemard L, Thouvenot D, Jagneaux V, Poitevin F, Malcus C, et al. Aerosol administration of a recombinant adenovirus expressing CFTR to cystic fibrosis patients: a phase I clinical trial. Hum Gene Ther 1997;8(1):15–25.
49. Flotte TR, Carter BJ. In vivo gene therapy with adeno-associated virus vectors for cystic fibrosis (review). Adv Pharmacol 1997;40: 85–101.
50. Naldini L, Blomer U, Gallay P, Ory D, Mulligan R, Gage FH, et al. In vivo gene delivery and stable transduction of nondividing cells by a lentiviral vector. Science 1996;272(5259):263–267.
51. Gill DR, Southern KW, Mofford KA, Seddon T, Huang L, Sorgi F, et al. A placebo-controlled study of liposome-mediated gene transfer to the nasal epithelium of patients with cystic fibrosis. Gene Ther 1997;4(3):199–209.
52. Eastman SJ, Lukason MJ, Tousignant JD, Murray H, Lane MD, St George JA, et al. A concentrated and stable aerosol formulation of cationic lipid: DNA complexes giving high-level gene expression in mouse lung. Hum Gene Ther 1997;8(6):765–773.
53. Pillai R, Petrak K, Blezinger P, Deshpande D, Florack V, Freimark B, et al. Ultrasonic nebulization of cationic lipid-based gene delivery systems for airway administration. Pharm Res 1998;15(11):1743–1747.
54. Stern M, Caplen NJ, Browning JE, Griesenbach U, Sorgi F, Huang L, et al. The effect of mucolytic agents on gene transfer across a CF sputum barrier in vitro. Gene Ther 1998;5(1):91–98.
55. Gendler SJ, Spicer AP. Epithelial mucin genes (review). Annu Rev Physiol 1995;57:607–634.
56. Rubin BK. Emerging therapies for cystic fibrosis lung disease (review). Chest 1999;115(4):1120–1126.

Methods of Calculating Lung Delivery and Deposition of Aerosol Particles

Chong S Kim PhD

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  Ultrafine Aerosols
  Polydisperse Aerosols
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Summary

[Respir Care 2000;45(6):695–711] *Key words: aerosol, deposition, scintigraphy, single photon emission computed tomography, SPECT, particle, photometry.*

Introduction

Deposition site and dose of inhaled drug aerosols vary widely within the lung, depending primarily on particle size, inhalation pattern, and lung structure. Generally, particles deposit more in the proximal airways with an increase in particle size and flow, whereas enhanced pulmonary deposition takes place with small size particles and slow flow.[1–6] Within the bronchial airways, particle deposition tends to localize at and near the carina, particularly with particles > 1 μm in diameter.[7–11] In patients with obstructive airway disease, deposition patterns are very heterogeneous and marked by pronounced deposition in the central airways and local "hot spots" in various regions of the lung.[12,13] Compared to normal subjects, overall lung deposition is higher in patients with obstructive airway diseases such as asthma and chronic bronchitis.[14–18] All of these aspects of lung deposition are important factors to consider in designing a drug aerosol delivery system.

Inhalation has been used successfully as a convenient and effective mode of delivery for many bronchodilators and corticosteroids in the management of asthma. Recent advances in biotechnology have resulted in an array of new drugs (eg, insulin, peptides, antibiotics, and gene products) that have great potential to be delivered via the respiratory route. However, these new drugs are expensive and often highly potent, and their actions are site-specific, requiring a precise control of dose at the specific site of action. Accuracy and precision both in methods of aerosol delivery and lung dose estimation have become more important now than ever before.

Conventionally, lung deposition is assessed by measuring the amount of aerosol inhaled and subsequently exhaled by means of either an on-line aerosol detector or filter sampling.[19,20] These methods provide information on nonspecific overall lung dose of aerosols under a variety of inhalation conditions. The information can be used to identify optimal inhalation or delivery conditions (eg, particle size and breathing pattern) to achieve a desired level of lung deposition. Gamma scintigraphy has been a primary method for measuring regional lung deposition. The method offers visual images that can be evaluated for dep-

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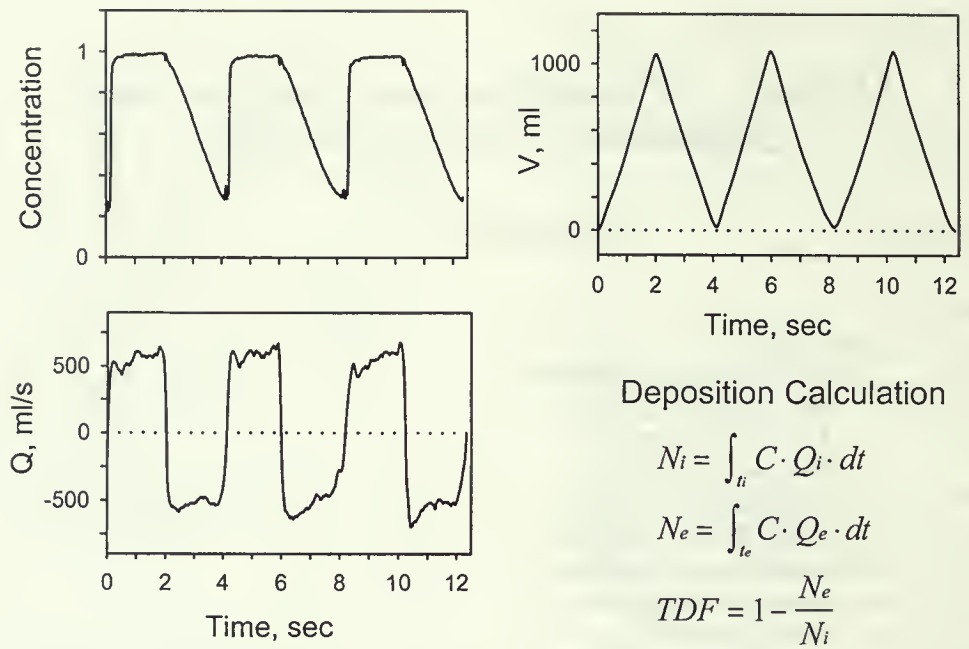


Fig. 1. Signals of aerosol concentration (C), flow (Q), and respired volume (V) simultaneously acquired and displayed breath by breath during inhalation, by on-line laser photometry system, and the calculation method used to determine total lung deposition fraction (TDF). N_i = total number of particles inhaled. N_e = total number of particles exhaled. Q_i = inspiratory flow. Q_e = expiratory flow. t_i = inspiratory time. t_e = expiratory time. dt = time differential.

osition patterns. However, planar scintigraphy has a limited ability for accessing specific regions of the lung, and the deposition pattern analysis is largely qualitative. Combined with particle clearance measurement, scintigraphy can measure specific regional deposition for tracheobronchial versus alveolar regions.[21–23] These deposition measurements have formed the basis of the current understanding of regional deposition. However, the two large regions may not satisfy the growing needs of site-specific deposition information. Recent advances in three-dimensional lung imaging technique such as single photon emission computed tomography (SPECT) and positron emission tomography (PET) offer a promise to measure detailed regional deposition.[24,25] Recently, an aerosol bolus method has been proposed to use for obtaining detailed regional deposition.[6,26] The method has potential for wide application because it does not require radioaerosols, and measurements are performed in situ. Current information on regional deposition is based largely on measurements in a small number of healthy subjects under a few controlled breathing conditions. This information cannot be freely extrapolated to the general population consisting of individuals with various lung conditions and breathing patterns. Experimental studies are difficult to perform for heterogeneous and unstable real aerosols. For these reasons, mathematical models are commonly used to obtain insights into detailed regional deposition in the lung under various inhalation conditions.[1–3,27–30] Clearly, an accurate measurement of regional lung dose is difficult to achieve by the conventional methods. A multi-pronged approach may be needed, with various methods and techniques, both in theory and experiment, to obtain site-specific deposition dose. This article reviews the current and emerging methods of lung deposition measurement relevant to medicinal aerosols.

Total Respiratory Deposition

Supramicron Aerosols

Total respiratory deposition is measured by monitoring both aerosol concentration (C) and volumetric flow ($\dot{Q}$) at the mouth during inhalation. By integrating the product of C and $\dot{Q}$ over the inspiratory and expiratory time, the total number of particles inhaled (N_i) and subsequently exhaled (N_e) is calculated breath-by-breath. Total deposition fraction (TDF) of aerosol is then determined by $1 - N_e/N_i$ (Fig. 1). By automating the inhalation system by means of on-line data acquisition and analysis, deposition values can be obtained immediately after inhalation. This allows measurement of lung deposition with a variety of breathing patterns in a relatively short period of time and determination of optimal inhalation conditions for a given aerosol. A measurement system typically consists of a laser aerosol detector, a pneumotachograph, a signal modulator, a pneumatic or solenoid three-way valve, and a computer (Fig.

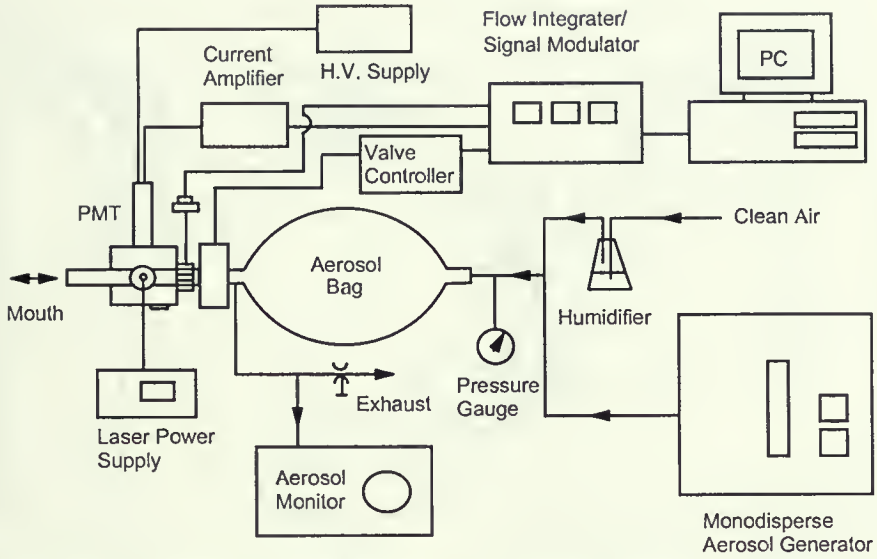


Fig. 2. Typical experimental setup for measuring total lung deposition of monodisperse aerosols using a laser aerosol detector. H.V. = high voltage. PMT = photomultiplier tube

2). A desired breathing pattern (ie, tidal volume [V_T], inspiratory and expiratory flow) is displayed on the computer screen for a subject to follow. Under the photometric mode, the laser aerosol detector measures total scattered light from a cloud of aerosol, and the level of output signals from the detector is proportional to the number concentration of aerosol for monodisperse aerosols. Using this method, total lung deposition has been measured for a wide range of particle sizes and breathing patterns,[20,31–34] and the relationships between total lung deposition and the factors affecting the deposition have been analyzed.[33,34]

Total lung deposition values (TDF), when plotted against particle size, form a U-shape curve with a minimum deposition at a particle diameter (d_p) around 0.5 μm (Fig. 3). This can be explained by the fact that particles deposit primarily by 3 mechanisms (inertial impaction, gravitational sedimentation, and diffusion) and that none of these mechanisms are acting strongly on particles of $d_p = \sim 0.5$ μm. Particles $< d_p = 0.5$ μm deposit effectively by diffusion, and particles $> d_p = 0.5$ μm deposit by inertial impaction and sedimentation. It should be noted in Figure 3 that the TDF curve shifts up and down depending on breathing pattern, but the position of minimum deposition remains at the same particle size regardless of breathing pattern. The relationship of each of the key breathing variables to TDF is illustrated in Figure 4 and Figure 5. It can be seen that TDF can vary by as much as 3 times, depending on breathing pattern, under normal tidal breathing conditions. With a constant flow, TDF increases with increasing V_T for all particle sizes (see Fig. 4). This is expected because, with a larger V_T, particles can penetrate deeper into the lung, where airway dimensions are small (ie, shorter deposition distance) and also stay longer in the lung. However, if the breathing frequency or respiratory time is fixed, TDF increases with increasing V_T for larger particles (ie, $d_p > \sim 2$ μm). The increase is small or negligible for particles with $d_p \leq 1$ μm; (see Fig. 5). For a given V_T, TDF decreases with an increase in breathing frequency (or flow) for smaller particles (ie, $d_p \leq \sim 3$ μm), but changes are small or negligible for larger particles (ie, $d_p \geq 5$ μm). This is because smaller particles deposit primarily by diffusion or gravitational sedimentation, which is governed by respiratory time. Faster breathing decreases respiratory time and decreases lung deposition of small particles. However, larger particles deposit by both sedimentation and inertial impaction. With a faster breathing rate, decreased deposition by sedimentation is compensated by increased deposition by inertial impaction, resulting in virtually no change in deposition of larger particles. The varying relationships of TDF with individual deposition factors can be unified when TDF is plotted against a single composite variable consisting of d_p, $\dot{Q}$, and V_T.[33,34] For example, TDF of particles in the 1–5 μm range may be expressed as $TDF = 1 - 1/(1 + \omega)$, where $\omega = 0.21 d_p^{1.61} \dot{Q}^{-0.37} V_T^{1.32}$ (Fig. 6). This empirical fitting curve is useful for estimating TDF under various inhalation conditions and provides a practical guide for selecting a proper breathing pattern for delivering a desired dose of aerosol to the lung.

Under the same breathing condition, TDF has been shown to be greater by ~10% in women than in men,[6,32] but age (range = 18–70 years) appears to have no effect on lung deposition among adults.[15,32] Therefore, the deposition relationships described above may be applied to healthy men and women in general, but these results cannot be extrapolated to patients with obstructive airway disease. TDF is expected to increase in lungs with obstructed airways be-

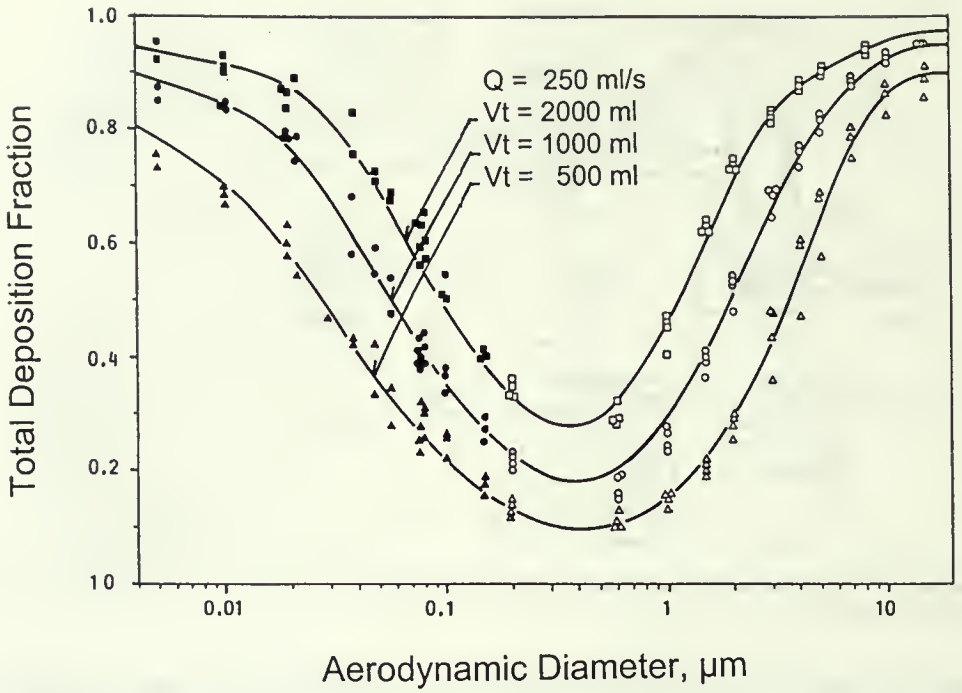


Fig. 3. Total lung deposition versus particle size for three different breathing patterns. V_T = tidal volume. Q = respiratory flow. (Adapted from Reference 22, with permission.)

cause inertial impaction becomes more efficient in the narrowed airways. A reduced airway volume, together with asymmetric ventilation pattern, also causes a deeper penetration of aerosols into the peripheral region of the lung, where deposition efficiency of sedimentation and diffusion is high. For particles with d_p = 1 μm, TDF is 59% greater in asthmatics and 103% greater in patients with chronic obstructive pulmonary disease than in normal subjects (Fig. 7).[17] Because particle deposition tends to be localized in lungs with obstructive airway disease, an increase in local dose can be much greater than that of TDF. Although TDF alone has limited utility for assessing local deposition doses in the regions of interest, a systematic analysis of TDF values obtained with different breathing patterns (eg, a stepwise increase in V_T) may provide insights into regional variations in deposition. It should also be noted that the results discussed above are based on inhalation of nonhygroscopic, stable, and monodisperse aerosols under normal tidal breathing patterns. Size characteristics and the mode of delivery of drug aerosols may not conform with these conditions. Lung deposition of drug aerosols has to be evaluated under specific delivery conditions used for the aerosols (see discussions below).

Ultrafine Aerosols

Because light scattering is not effective for small particles, the conventional in-line laser aerosol detector is not suitable for detecting ultrafine particles. However, lung deposition of ultrafine particles can be measured breath-by-breath by using an ultrafine condensation particle counter (eg, model 3025, TSI Inc, St Paul, Minnesota). In this method, inhalation setup is essentially the same as that used for supramicron aerosols except that a small portion of aerosol is continuously sampled into the condensation particle counter from the mouthpiece during inhalation. In the ultrafine condensation particle counter, aerosol particles are mixed with alcohol vapor and then pass through a condenser column in which alcohol vapor condenses on the surface of particles. As a result, ultrafine particles grow to supramicron size and the enlarged particles are detected by the conventional laser aerosol detector.[35,36] Using this method, Jaques and Kim[37] recently measured total lung deposition in healthy men and women under several different tidal breathing conditions. Their results are summarized in Figure 8. The figure shows that the TDF of ultrafine particles increases with a decrease in particle size and with breathing patterns of longer respiratory time. The deposition relationship is consistent with diffusion deposition expected by theory. Note that breath-by-breath measurement of lung deposition requires a fast-response aerosol monitor (eg, time constant $\ll$ respiratory time). For aerosol detectors with slow response times, exhaled aerosols need to be collected in a bag for a number of breaths and then measured by the detector. TDF is then determined by the ratio of the exhaled to inhaled aerosol con-

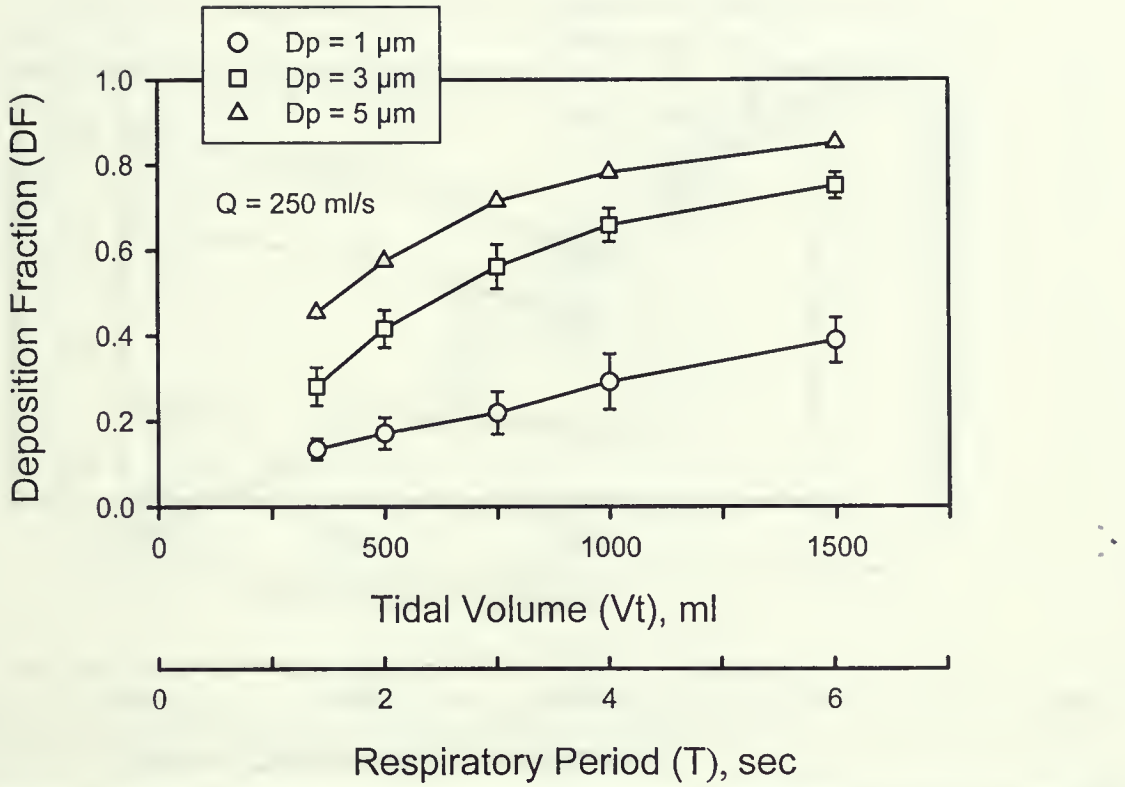


Fig. 4. Total lung deposition versus tidal volume and respiratory time at a fixed value of flow. Respiratory flow = 250 mL/s. Dp = particle diameter.

centration after correcting for particle losses in the bag. This method has been used in several earlier studies.[38–42] Lung deposition may also be determined by collecting inhaled and exhaled aerosols on filters. Aerosol mass collected on the filters is usually very small (eg, < 1 μg) and gravimetric analysis of the samples is often unwarranted. However, aerosol mass can be determined by analyzing a specific chemical component of particles or a labeled agent (eg, fluorescence or radionuclide) that can be measured accurately at very low concentrations.[43,44] Ultrafine particles are ubiquitous in the air and their role in potential health effects is highly scrutinized. However, from the drug delivery point of view, ultrafine aerosols may have limited applications, because of the difficulties of producing stable ultrafine particles on the one hand and a very low-mass dose (ie, < 1 μg) available for lung deposition on the other hand (see Table 1).

Polydisperse Aerosols

Aerosols, natural or man-made, including drug aerosols, are normally polydisperse. Because the laser photometric method discussed above can be applied only to monodisperse aerosols, it cannot be used for on-line measurement of polydisperse aerosols. Ideally, lung delivery and deposition of polydisperse aerosols can be assessed by measuring the complete size distribution of both inhaled and exhaled aerosols. However, a measurement of complete size distribution takes much longer than a respiratory period, making on-line measurement of polydisperse aerosols impossible. Conventional methods collect exhaled aerosols into a bag for a number of breaths and subsequently measure the size distribution. This process often results in loss of particles. Because the losses are not the same for particles of different sizes, this can alter the size distribution of the aerosols. Exhaled aerosols also are subjected to high humidity, which can be detrimental to particle size analysis. If the particles are hygroscopic, experimental difficulties are further elevated. For these reasons, systematic experimental studies have been hampered, and detailed lung deposition of polydisperse aerosols is analyzed primarily by mathematical models.[28,45] Generally, mathematical models predict that total lung deposition increases with increasing polydispersity (ie, geometric standard deviation, σ_g) for aerosols with a mass median aerodynamic diameter (MMAD) between 0.05 μm and 3 μm, but the effect is the opposite for aerosols with MMAD < 0.05 μm or MMAD > 3 μm (Fig. 9). The effects of σ_g appear to be maximum at MMAD = 0.5–1 μm. Studies by Diu and Yu[28] have shown that total lung deposition is increased by

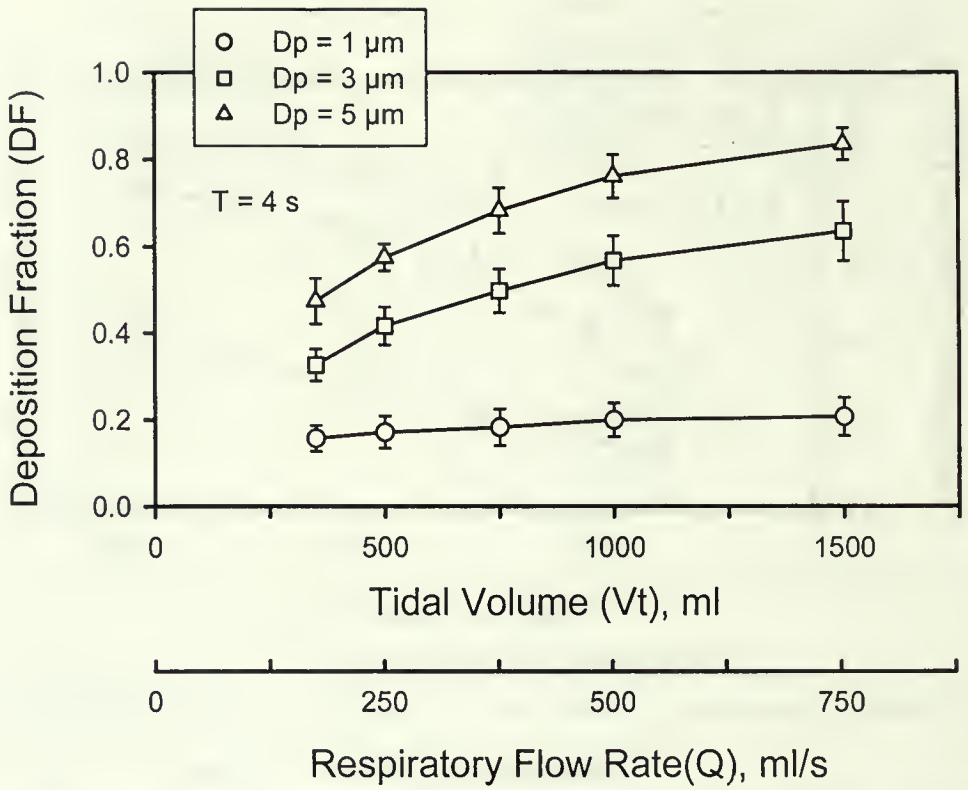


Fig. 5. Total lung deposition versus tidal volume and respiratory flow at a fixed value of respiratory time (4 s) or breathing frequency (15 breaths/min). Dp = particle diameter.

approximately 19%, 83%, and 137% as σ_g is increased from 1 to 1.5 to 2.5 to 3.5, respectively, when the aerosol is inhaled at a V_T of 1,000 mL and a breathing frequency of 15 breaths per minute. However, it is interesting to note that because of the crossover effect of σ_g at MMAD = ~3 μm, lung deposition of polydisperse aerosols, regardless of σ_g values, may not be much different from that of monodisperse aerosols at MMAD of ~3 μm. The pharmaceutical aerosols commonly used for respiratory delivery have MMADs of 1–3 μm and σ_g of 2.0–2.5.[46,47] Lung deposition of these aerosols is expected to be greater than those of monodisperse aerosols. However, the degree of deposition increase may vary depending on the individual's lung condition (ie, small vs large and normal vs diseased) and the mode of inhalation.

Although an automatic in-line measurement of polydisperse aerosols may not be possible during inhalation, filtration methods are commonly used for determining lung deposition of polydisperse aerosols.[43,44] In this method, aerosols are inhaled via a one-way valve from the inspiratory line and exhaled through a filter via another one-way valve. A pneumatic or solenoid three-way valve may be used instead of two one-way valves. During inhalation, aerosols also are sampled on a filter from the inspiratory line. Total lung deposition is determined by comparing the aerosol masses collected on the inspiratory and expiratory filters. In analyzing filter samples, the gravimetric method is seldom used, particularly for pharmaceutical aerosols, because of hygroscopicity problems. Filter analysis is commonly performed for a specific drug compound for pharmaceutical aerosols. If necessary, aerosols can be labeled with a specific chemical agent or radionuclide that can be measured conveniently and accurately, as discussed above. Aerosol mass may then be determined by the assay of those specific agents.

Hygroscopic Aerosols

Most drug aerosols are not only polydisperse but also hygroscopic to some degree. Hygroscopic growth of particle size can be measured under controlled humidity conditions in vitro.[46,47] Once the growth characteristics of aerosols have been determined, lung deposition may be estimated from the deposition data of nonhygroscopic aerosols. Here, one should note that hygroscopic growth of particles does not always cause an increase in lung deposition. Because total lung deposition values form a U-shaped curve with respect to particle size (see Fig. 3), deposition of hygroscopic particles may increase or decrease depending on the initial particle size of the aerosols (Fig. 10). Many drug aerosols exhibit substantial hygro-

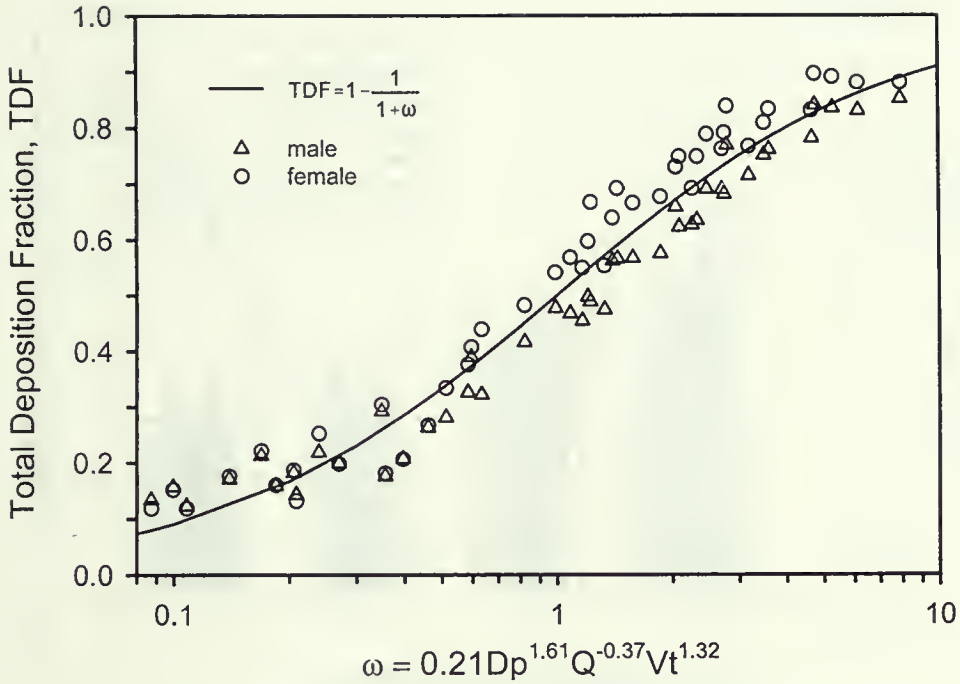


Fig. 6. Total lung deposition versus a composite inhalation variable. Symbols represent deposition values obtained with 12 different breathing patterns for particles 1–5 μm in diameter. Note that varying deposition values can be unified by a single deposition variable. Dp = particle diameter (μm). Q = respiratory flow (L/s). V_T = tidal volume (L).

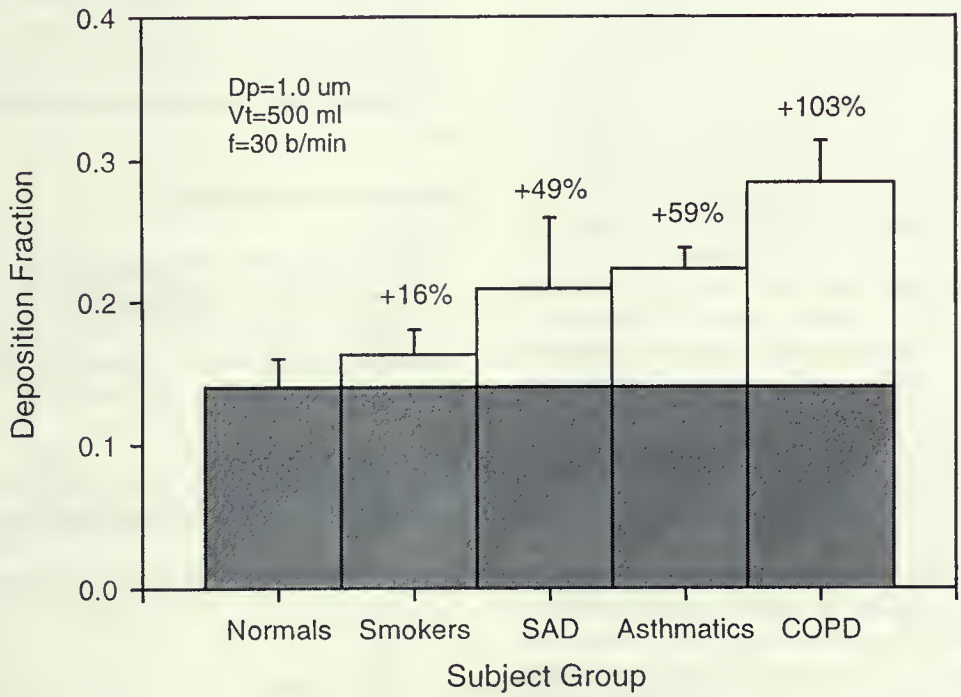


Fig. 7. Total lung deposition of a fine aerosol (particles 1 μm in diameter) in healthy adults and subjects with obstructive airway disease. The numbers shown over the bars indicate percent increase above normal values. SAD = smoker with symptoms of small airway disease. COPD = patients with chronic obstructive pulmonary disease. Dp = particle diameter. V_T = tidal volume. f = respiratory rate. (Adapted from Reference 17.)

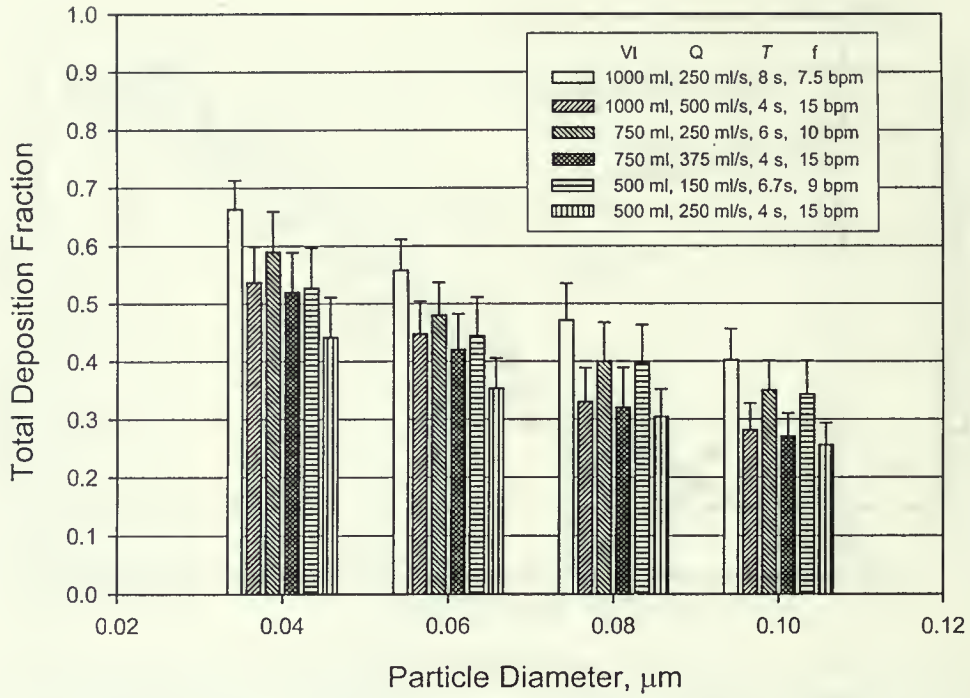


Fig. 8. Total lung deposition of ultrafine particles in healthy adults under various inhalation conditions. Each bar represents mean ± SD of 22 subjects. V_T = tidal volume. Q = respiratory flow. T = time. f = respiratory rate. bpm = breaths per minute. (From Reference 37, with permission.)

scopic growth, particularly with an initial particle size in the range of 0.5–2 μm. Lung deposition of these drug aerosols may increase by as much as a factor of two (see Fig. 10).[29,30] Experimental data on lung deposition of hygroscopic aerosols are scarce and are based largely on a few studies using dry monodisperse NaCl aerosols.[38,39] Results from these studies generally support the dichotomous effect of hygroscopic growth on total lung deposition. The growth of particle size during inhalation may cause a substantial alteration of deposition sites within the lung. Deposition site may shift proximally with particle growth. This is particularly true for dry aerosols with strong hygroscopicity, such as cromolyn sodium.[47] The proximal shift of deposition site can be beneficial for drugs targeted for the airways, but can be a serious problem for drugs that must be delivered to the pulmonary region. Depending on the desired target site, the hygroscopic growth of particle size may be controlled or prevented by coating the surface of particles with a hygroscopic or hydrophobic film.[48] Although total lung deposition of hygroscopic aerosols can be measured by filter collection methods, as discussed above, deposition sites are difficult to determine. Many mathematical models have been proposed to analyze the growth and deposition characteristics of hygroscopic aerosols in the lung, particularly for dry salt aerosols.[49,50] Deposition predictions of hygroscopic liquid aerosols (eg, NaCl solution) are more complex because the growth of liquid particles involves a two-way coupled process of evaporation and condensation. The deposition estimates may vary significantly, depending on the particle growth kinetics used for modeling.[29,51–52] Recent studies using a two-way coupled analysis of concentrated droplet aerosols suggest that the hygroscopic effect may be minimal for most liquid aerosols generated by commonly-used medical nebulizers.[53]

Single-Breath Inhalation

Aerosols are often delivered during a single-breath inhalation, as with metered-dose inhalers. A typical inhalation mode is a maximal inspiration followed by breath-holding for a few seconds, then slow exhalation. Under this inhalation condition, lung deposition is much greater

Table 1. Mass Concentration of Ultra-Fine Aerosols

Particle Diameter (mm)	Mass Concentration* (μg/L)
0.01	5.23×10^{-4}
0.05	6.54×10^{-2}
0.10	5.23×10^{-1}
0.50	6.54×10^{1}
1.00	5.23×10^{2}

*Based on the number concentration of 10^7 per cm^3 and particle density of 1 g/cm^3.

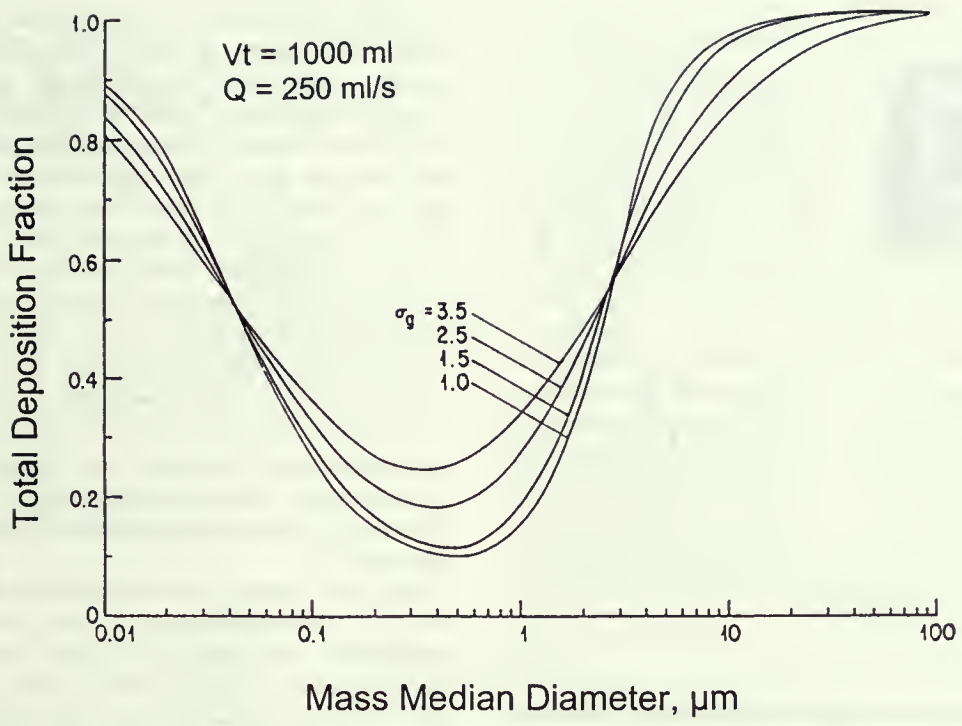


Fig. 9. Mathematical model prediction of total lung deposition of polydisperse aerosols characterized by a log-normal distribution with 4 different levels of dispersity. σ_g represents the geometric standard deviation of particle diameter. V_T = tidal volume. Q = respiratory flow. (Adapted from Reference 28, with permission.)

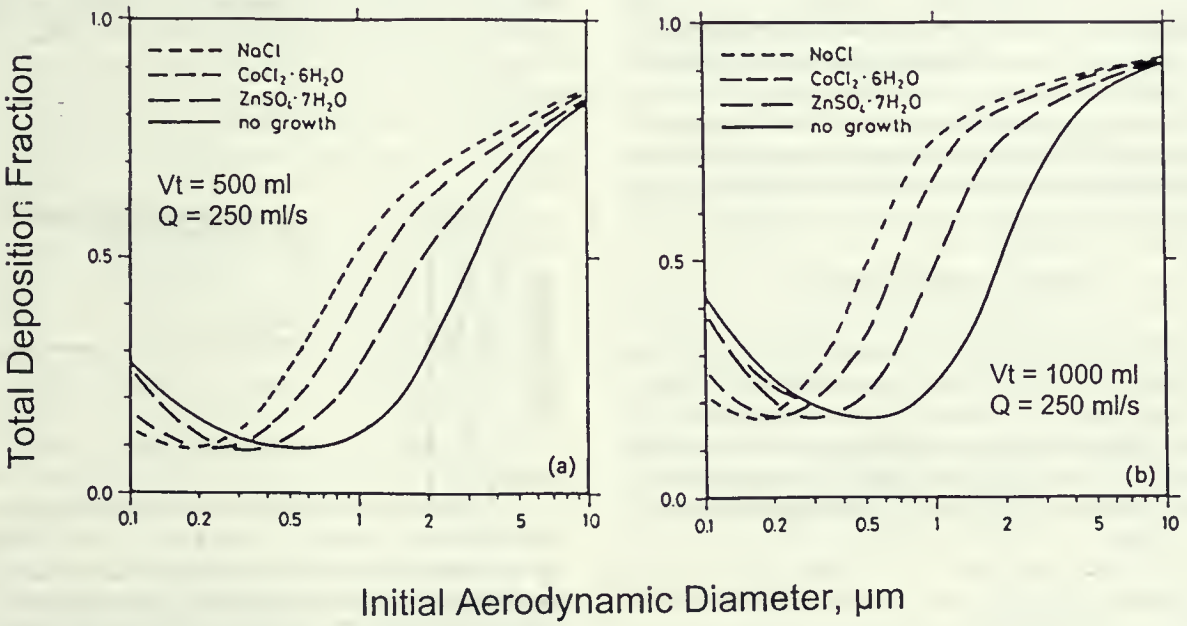


Fig. 10. Mathematical model prediction of total lung deposition of hygroscopic aerosols of different growth characteristics under two different breathing conditions. Tidal volume (V_T) of 500 mL (left panel) and 1,000 mL (right panel) at a flow of 250 mL/s. Q = respiratory flow. (Adapted from Reference 50, with permission.)

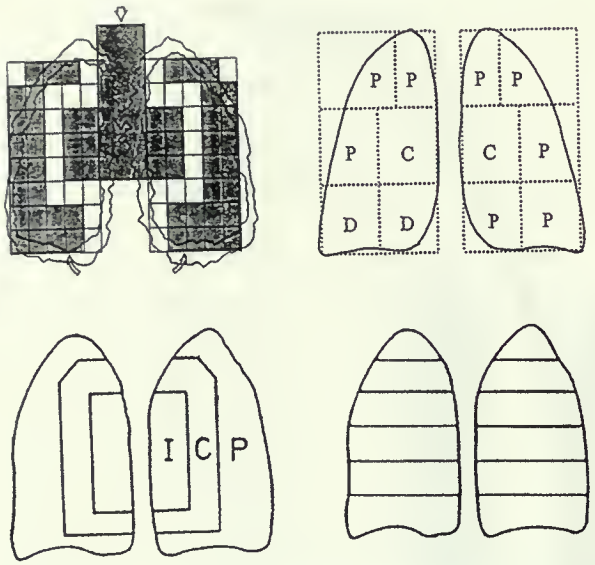


Fig. 11. Various methods of analyzing deposition patterns in the lung using scintigraphic lung images.

than that expected under normal tidal breathing conditions. For example, for small (ie, 1.5 μm) particles, total lung deposition reaches almost 90% after 5 seconds of breath-holding at the end of a single inhalation of 2 L aerosol.[54] An equally high lung deposition (70–94%) can be obtained even without breath-holding if aerosols are inhaled maximally to the total lung capacity.[55] A maximal inhalation of larger-particle aerosol can result in a 100% deposition without breath-holding.[56] It should be noted that in most single-breath inhalation methods used for delivering drug aerosols, the aerosols are delivered as a pulse or bolus in the beginning phase of an inspiration, as with metered-dose inhalers. In this case, aerosols are delivered mostly to the deep lung regions, and deposition is almost guaranteed to be 100%.[26,57] Therefore, total lung deposition may not be an important issue in the single breath inhalation method, but the sites of deposition are still of concern.

Regional Lung Deposition

Unlike total lung deposition, measuring regional or local deposition is a difficult task to accomplish. The difficulties arise from the fact that positive identification of specific anatomic sites within the lung cannot be achieved accurately by current methods. Innovative ideas and approaches are needed to assess regional deposition of inhaled particles.

Gamma Scintigraphy

In this method, aerosol particles are usually labeled with a gamma-emitting radionuclide (eg, ^{99m}Technetium). Immediately after inhalation of the labeled aerosols, scintigraphic lung images are obtained by a large-face gamma camera. Traditionally, the lung images are examined to assess the qualitative nature of deposition pattern (ie, whether the deposition pattern is even or uneven, or if there are any unique deposition characteristics such as local "hot spots"). The visual examination is usually sufficient for the purpose of comparing normal and diseased lungs, or pretreatment versus posttreatment condition of lungs, or one inhalation condition (eg, particle size, breathing pattern, delivery device) versus another. The method has been used extensively in nuclear medicine as a diagnostic tool for assessing obstructive airway disease.[12,13] The method is also useful for studying optimal delivery of drug aerosols, and particularly for documenting desirable or undesirable deposition patterns of delivered aerosols (ie, marked oropharyngeal deposition of pressurized MDI aerosols).[58,59]

Regional deposition patterns can be analyzed quantitatively by gamma scintigraphy. In this method, the planar scintigraphic lung images are divided into a number of small compartments (ie, regions of interest) and the activities from each compartment are measured. The compartmental division can be arranged in the form of square grids, or concentric rings, or any desired shapes (horizontal or vertical divisions) (Fig. 11). Evenness or unevenness of deposition pattern can be expressed by variations of activity count in each compartment.[60–62] However, the planar images have a fundamental limitation in analyzing three-dimensional objects with irregular shapes. The actual lung volumes projected on each planar compartment vary widely, and each compartment cannot be related to specific anatomic regions. Within these limitations, planar scintigraphy has been used to describe relative deposition between different lung compartments (ie, central or inner

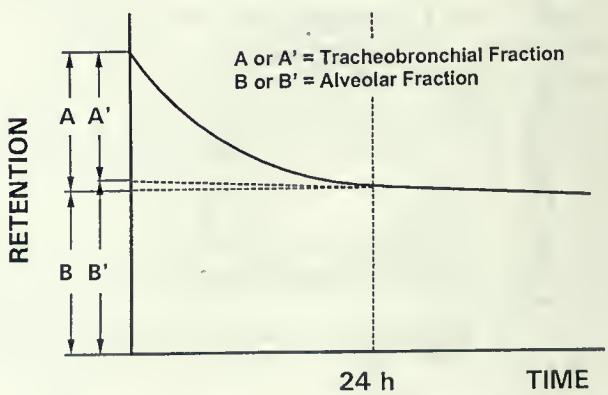


Fig. 12. Method of determining tracheobronchial versus alveolar deposition in the lung by measuring the retention activity of particles as a function of time. A: y-intercept of horizontal extension of 24-hour retention value. A': y-intercept of extension of the slope of post-24-hour retention curve. A or A' is used, depending on investigator. Difference between A and A' is usually very small.

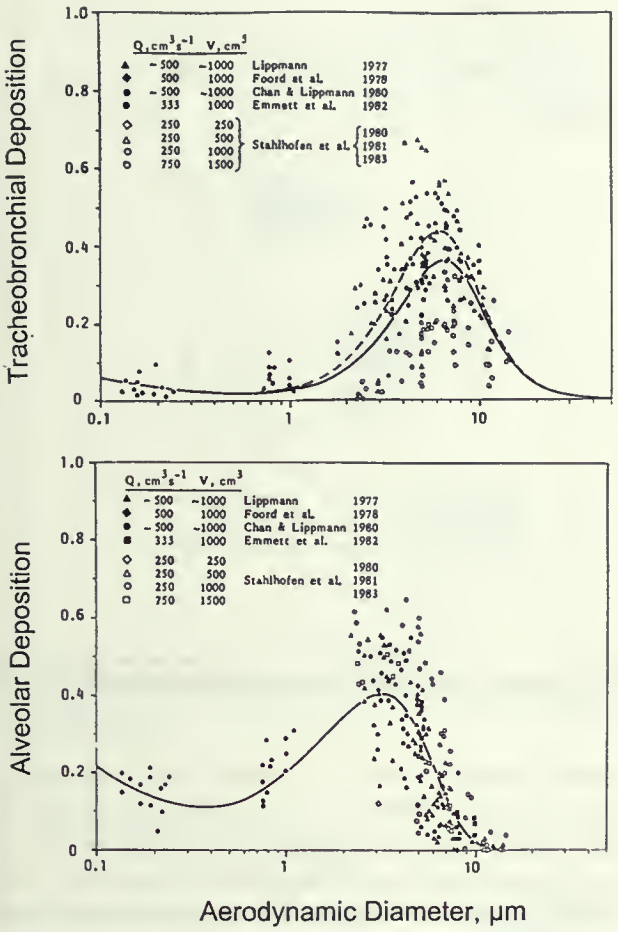


Fig. 13. Regional deposition in the tracheobronchial and alveolar regions of human lungs determined by scintigraphic method described in Figure 12. Q = respiratory flow. (Adapted from Reference 22, with permission.)

zone versus peripheral or outer zone). In this method, planar lung images of radioactive gases (eg, ^{133}Xenon or ^{81m}Krypton) are used to define the central (C) versus peripheral (P) zone, and activity counts are obtained from each zone by gamma camera. The procedure is then repeated with aerosols. The ratio of activity count in the central to peripheral zone (C/P ratio) is calculated for aerosols and normalized by the C/P ratio of gas images. The ratio of C/P (aerosol) to C/P (gas) is defined as the specific C/P ratio (sC/P), or simply C/P ratio.[63–65] The inverse of the C/P ratio is often termed the "penetration index" or "aerosol penetration."[64,65] Here, a C/P ratio of 1 indicates a fairly uniform deposition pattern, as in distribution of a gas. A C/P ratio of $>$ 1 indicates greater central deposition. The C/P ratio has been used to conveniently express deposition patterns, particularly in studies investigating the different roles of the conducting airways and pulmonary regions in aerosol delivery, deposition, and clearance.[66]

Radiolabeled aerosols are also used to obtain regional deposition values in the classical three-compartment lung regions. Immediately after inhalation of radiolabeled aerosols, the radioactivity in the head region (larynx and above) and in the lung is measured either by a gamma camera or whole body counter. The lung activity is then measured periodically over a period of 24–48 hours.[23,67] From the lung activity versus time curve, deposition fraction in the tracheobronchial airways is determined based on the premise that particles deposited in the tracheobronchial airways are cleared out completely from the lung within 24 hours by the mucociliary escalator. The portion of the activity remaining in the lung after 24 hours is considered the alveolar fraction (Fig.12). Thus, the traditional three-compartment respiratory deposition information is obtained: head or extrathoracic region, tracheobronchial region, and alveolar region.[4,5,21,22,68] The current information on regional lung deposition is almost entirely based on the data obtained by this method, and the data summarized by Stahlhofen et al[22] are shown in Figure 13. In Figure 13, notice that there is a large variation of data. One of the reasons for the variation is that the data include results obtained with different inhalation conditions (eg, range of V_T = 250–1,500 mL). Another reason may be that different investigators use different methods for correcting tissue attenuation of radioactivity. Most of all, because the accuracy of these measurements largely depends on particle clearance rate from the tracheobronchial airways, this limits applications of the method to only those with normal mucociliary function. The method may not be used for patients with impaired mucociliary function.

Single Photon Emission Computed Tomography and Positron Emission Tomography

Although specific sites of deposition may not be obtained by the conventional two-dimensional lung imaging, recent advances in three-dimensional imaging techniques such as SPECT show great potential for measuring local dose of particles in specific sites in the lung.[24,25] Basically, SPECT maps the three-dimensional concentration of a radionuclide (eg, ^{123}Iodine or ^{99m}Technetium) within an organ by measuring the intensities of gamma rays emitted by small-volume elements (voxels). The size of a voxel ranges from 0.3 cm^3 to 0.6 cm^3 for a typical scanning matrix. SPECT imaging is usually performed by a rotating gamma camera acquiring 64 projection views with a 360° rotation. The data acquisition time ranges from 10 to 30 seconds per view at the activity count rate of 2,000 counts per minute, which is considered the minimum dose required for obtaining quality images. A complete three-dimensional lung scan may take 5–10 minutes, depending on the camera configuration. A SPECT system can then produce multiple images of contiguous transverse and longitudinal sections

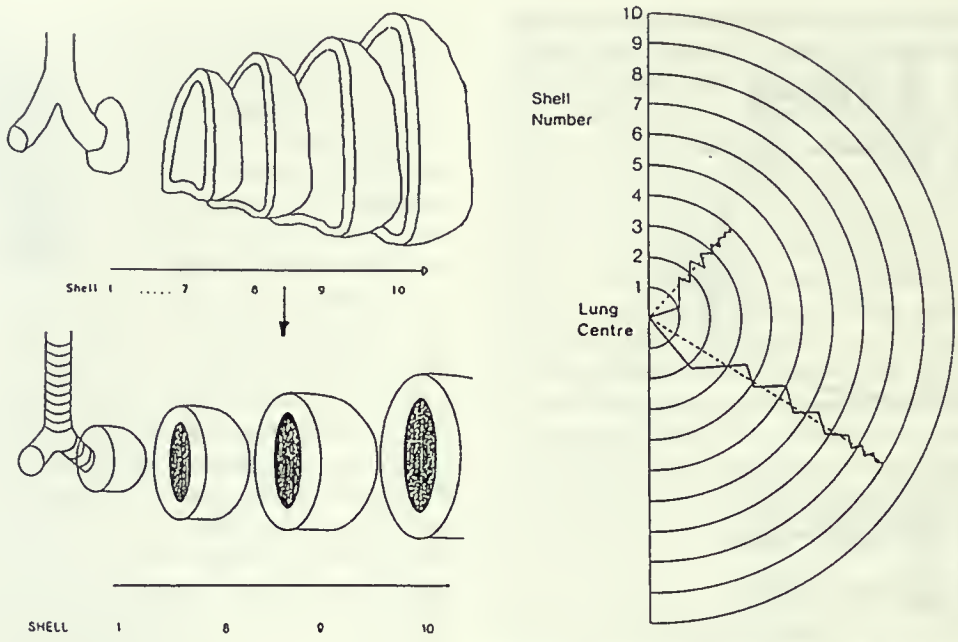


Fig. 14. Transformation of single photon emission computed tomography (SPECT) data to a hemispheric shell lung model (left panel), and a method of identifying airway generations in the three-dimensional shell lung model (right panel). (Adapted from References 72, with permission.)

from the acquired activity profiles. SPECT has been shown to be superior to planar imaging in spatial resolution and ideal for obtaining accurate measurement of regional deposition dose.[69–71] Studies have shown that SPECT is capable of discriminating aerosol deposition in small airways versus large airways.[70] Activity distributions on the transverse sections of the lung obtained by SPECT has been shown to be comparable to that of x-ray computed tomography.[71] However, the value of SPECT images cannot be fully realized unless the three-dimensional images are related to a realistic lung morphology such that specific anatomic sites can be identified. In studies by Fleming et al,[72,73] SPECT deposition data were transformed to a conceptual lung model consisting of a series of hemispherical shells that, in turn, incorporated a three-dimensional structure of Weibel's airway model (Fig.14).[74] From this complex transformation model, deposition values have been obtained for individual airway generations.[75,76] The accuracy of the results has yet to be proved, and the studies are far from completion. However, the approach has great potential for accurate assessment of regional deposition.

PET is used in association with a special class of unstable radionuclides (eg, ^{11}Carbon, ^{13}Nitrogen, and ^{18}Fluorine) that emit positrons.[77] The kinetic energy of the positrons is rapidly absorbed in adjacent tissue, normally within 1 mm of the emission. As a result of interaction with tissue electrons and subsequent annihilation, two 511 kiloelectron volt gamma rays are emitted in coincidence to each other. Detection of gamma rays in a PET scanner is based on the same principle as in a SPECT—viz, rotating gamma cameras. However, currently PET is not widely used, compared to SPECT, mainly because the half-life of positron-emitting radioisotopes is very short, which requires an expensive on-site accelerator for production. Use of PET in lung studies includes measurements of regional blood volume, regional lung density, regional ventilation, and ventilation-perfusion ratio.[77,78] Applications of PET to aerosol imaging have yet to be explored.

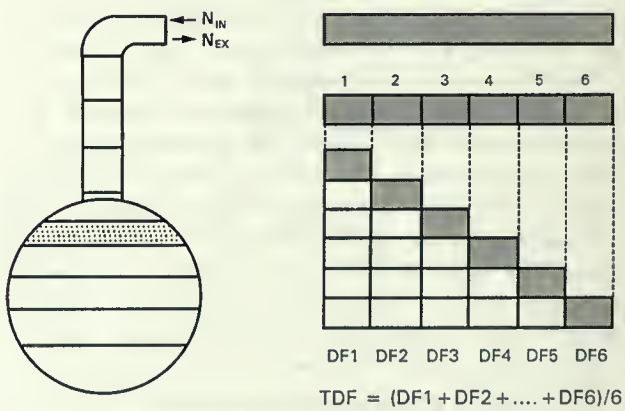
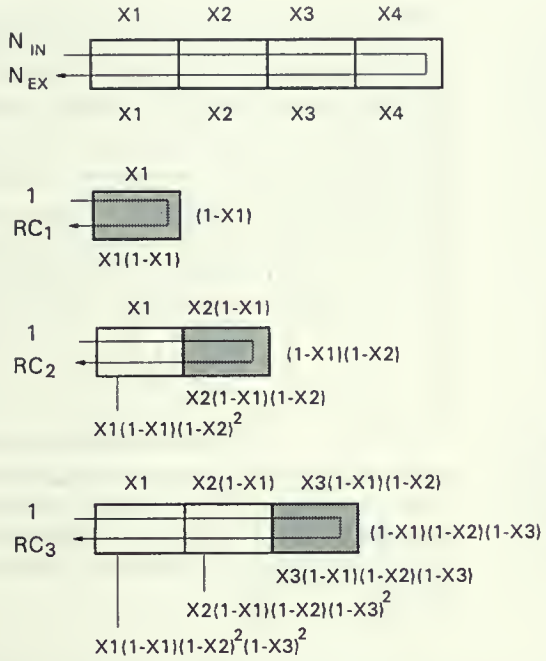


Fig. 15. Schematic diagrams illustrating principles of a serial bolus delivery method used for measuring regional deposition in human lungs. A tidal volume (V_T) is divided into a number of smaller volume compartments and a series of inhalations is performed with the same V_T but with an aerosol filled in only one compartment in each inhalation. TDF = total deposition fraction. DF = deposition fraction.



X: local deposition efficiency

$X(i) = N_{EX}(i) / N_{IN}(i)$

$RC = N_{EX} / N_{IN}$

$RC1 = (1-X1)^2$

$RC2 = (1-X1)^2 \cdot (1-X2)^2$

$RC3 = (1-X1)^2 \cdot (1-X2)^2 \cdot (1-X3)^2$

$$RC_n = \prod_{m=1}^{n} (1-X_m)^2$$

Fig. 16. Calculation scheme for regional deposition developed for analysis of a serial bolus recovery data. X = local deposition efficiency. RC = bolus recovery data at the mouth. N_{in} = total number of particles inhaled. N_{ex} = total number of particles exhaled. (From Reference 6, with permission.)

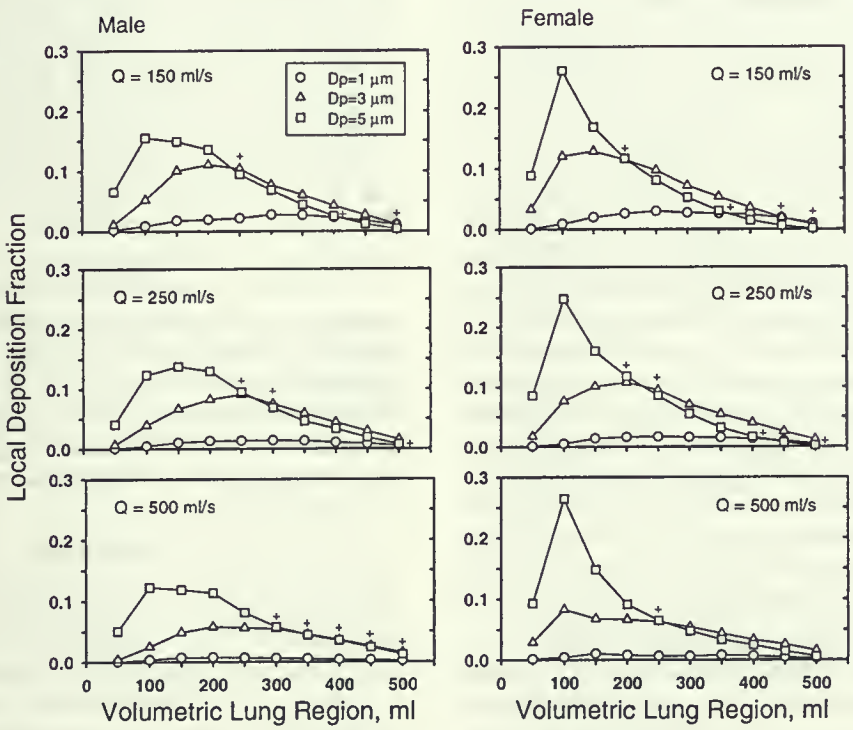


Fig. 17. Regional deposition distribution of monodisperse aerosols (1–5 μm in diameter) in the lungs of men (left panel) and women (right panel) breathing with a tidal volume of 500 mL and respiratory flow (Q) of 150, 250, or 500 mL/s. Note that deposition distribution is very uneven along the depth of the lung and peak deposition takes place in the shallow regions of the lung for coarse particles, but in the deeper lung regions for fine particles. Also note the difference between men and women. Dp = particle diameter. (From Reference 6, with permission.)

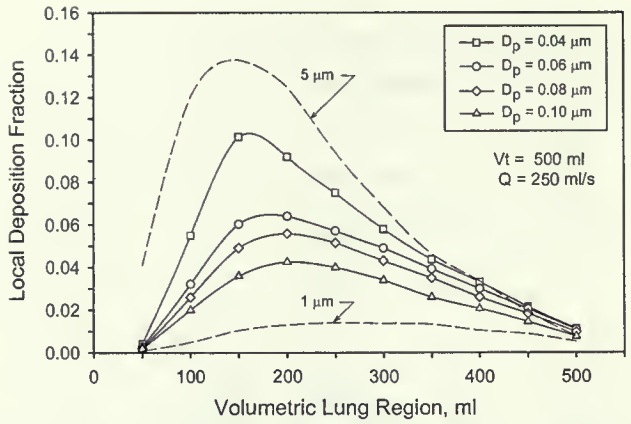


Fig. 18. Regional deposition distribution of ultrafine aerosols (0.04–0.1 μm in diameter) in healthy men breathing with a tidal volume of 500 mL and respiratory flow of 250 mL/s. Note that deposition patterns of ultrafine particles are confined between those of 1 μm and 5 μm particles. The site of peak deposition shifts proximally for smaller ultrafine particles.

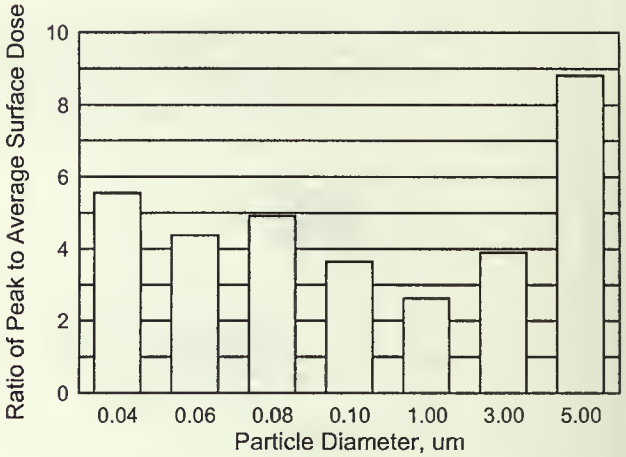


Fig. 19. Ratio of peak regional surface dose to the average surface dose plotted against particle diameter. Peak surface dose takes place in the region of 50–100 mL depth (shown in Fig. 18) and the peak surface dose is 3–9 times greater than the average surface dose of the whole lung.

Bolus Delivery Aerosols

For nonradioactive aerosols, a targeted delivery to a specific region of the lung and subsequent deposition in the local region can be obtained by means of bolus aerosol delivery method.[6,26] The method is based on the notion that a single inhalation of aerosol filled in the whole V_T is equivalent to a series of inhalations of small-volume aerosols that make up the V_T, as illustrated in Figure 15. Typically, the V_T is divided into 10 compartments of equal volume and a series of inhalations is performed with the same V_T, but with a bolus aerosol filling only one volumetric compartment in each inhalation. By analyzing the recovery data of bolus aerosols delivered to different depths of the lung in a sequential fashion, deposition efficiency and deposition fraction in each of 10 compartments can be calculated (Fig. 16). Theoretically, there is no limitation in the number of lung compartments that can be assessed. Because the bolus method does not require radiolabeled aerosols, the method may be applied to a broad spectrum of subject groups, both healthy persons and patients with lung disease. The method also allows repeated measurements in the same individuals, without concerns of potential health hazards from radioactivity. However, the bolus method has its own limitation in that lung regions are not positively identified, but rather inferred by the volume of air inhaled. Because the relationship between the inhaled volume and specific anatomic sites is not necessarily consistent among different individuals, interpretations of the bolus results may require careful consideration of the pathophysiological lung conditions of each individual.

Using this method, Kim et al[6,26] measured regional deposition in healthy young subjects for a wide range of particle sizes (d_p = 0.04–5 μm) under normal breathing conditions. In Figure 17, their results show that regional or local deposition in each of ten 50 mL volumetric compartments increases initially with volumetric lung depth (Vp) from the mouth, reaches the peak value, and then gradually decreases with a further increase in lung depth. The deposition pattern was consistent regardless of particle sizes and breathing patterns used. However, the peak height and position varied depending on particle size and breathing pattern. The peak deposition was found in the proximal airway region (Vp = 100–150 mL) for coarse particles (eg, d_p = 5 μm), and in the deeper lung regions (Vp = 250–300 mL) for fine particles (d_p = 1 μm). Sites of peak deposition of ultrafine particles were between those of d_p = 1 μm and 5 μm. However, within the ultrafine size range, peak deposition was found in the more proximal region with smaller particles, as shown in Figure 18. This indicates that deposition patterns of very small ultrafine particles are comparable to those of large coarse particles. In other words, ultrafine particles deposit in the lung more like coarse particles. It should also be noted that the surface area of the lung increases rapidly as the airways branch out into the deeper lung regions. Therefore, if regional deposition values are normalized by the surface area of each region, the surface dose becomes the largest in the most proximal lung region and decreases rapidly with an increase in Vp. The peak surface dose has been found to be 3–9 times greater than the average lung dose, depending on particle size (Fig. 19). The results have important implications for drug delivery—that overdosing of drug can occur at certain lung regions if drug dosing is determined by total lung deposition values. The regional deposition values obtained by the bolus method cannot be validated

for each compartment because there are no proven data available for regional deposition in such a detail as in the bolus method. However, from the 10-compartment results obtained by the bolus method, total as well as conventional three-compartment regional deposition can be determined and compared with conventional deposition data. Bolus results have shown good agreement with the conventional data in both total and three-compartment regional deposition, indicating that the bolus method is accurate and reliable for measuring regional lung deposition.

Summary

Lung deposition of aerosol is measured by a variety of methods. Total lung deposition can be measured by monitoring inhaled and exhaled aerosols in situ by laser photometry or by collecting the aerosols on filters. The measurements can be performed accurately for stable monodisperse aerosols. However, for polydisperse and/or unstable hygroscopic aerosols, measurement methods are limited and often unreliable. Regional deposition is assessed primarily by gamma scintigraphy. The scintigraphic method is useful for a general description of deposition patterns, but may not be adequate for quantitative regional dose estimation.

New emerging three-dimensional lung imaging methods such as SPECT and PET, and innovative bolus aerosol delivery methods, have great potential for measuring detailed regional deposition. An accurate assessment of regional lung dose is difficult to achieve by the current methods. A multi-prong approach may be needed, with various methods and techniques, both in theory and experiment, to measure site-specific deposition dose.

DISCLAIMER

Although the research described in this article was supported by the United States Environmental Protection Agency, it has not been subjected to Agency review and therefore does not necessarily reflect the views of the Agency and no official endorsement should be inferred. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

REFERENCES

1. Gerrity TR, Lee PS, Hass FJ, Marinelli A, Werner P, Lourenço RV. Calculated deposition of inhaled particles in the airway generations of normal subjects. J Appl Physiol 1979;47(4):867–873.
2. Yu CP, Diu CK. Total and regional deposition of inhaled aerosols in humans. J Aerosol Sci 1983;14:599–609.
3. Martonen TB, Katz IM. Deposition patterns of aerosolized drugs within human lungs: effects of ventilatory parameters. Pharm Res 1993;10(6):871–878.
4. Stahlhofen W, Gebhart J, Heyder J. Experimental determination of the regional deposition of aerosol particles in the human respiratory tract. Am Ind Hyg Assoc J 1980;41(6):385–398.
5. Chan TL, Lippmann M. Experimental measurements and empirical modeling of the regional deposition of inhaled particles in humans. Am Ind Hyg Assoc J 1980;41(6):399–409.
6. Kim CS, Hu SC. Regional deposition of inhaled particles in human lungs: comparison between men and women. J Appl Physiol 1998; 84(6):1834–1844.
7. Schlesinger RB, Bohning DE, Chan TL, Lippmann M. Particle deposition in a hollow cast of the human tracheobronchial tree. J Aerosol Sci 1977;8:429–445.
8. Schlesinger RB, Gurman JL, Lippmann M. Particle deposition within bronchial airways: comparisons using constant and cyclic inspiratory flows. Ann Occup Hyg 1982;26(1–4):47–64.
9. Kim CS, Iglesias AJ. Deposition of inhaled particles in bifurcating airway models. I. Inspiratory deposition. J Aerosol Med 1989;2:1–14.
10. Kim CS, Fisher DM, Lutz DJ, Gerrity TR. Particle deposition in bifurcating airway models with varying airway geometry. J Aerosol Sci 1994;25:567–581.
11. Kim CS, Fisher DM. Depositin characteristics of aerosol particles in sequentially bifurcating airway models. Aerosol Sci Technol 1999; 31:198–220.
12. Isawa T, Wasserman K, Taplin GV. Lung scintigraphy and pulmonary function studies in obstructive airway disease. Am Rev Respir Dis 1970;102(2):161–172.
13. Taplin GV, Tashikin DP, Chopra SK, Anselmi OE, Elam D, Calvarese B, et al. Early detection of chronic obstructive pulmonary disease using radionuclide lung imaging procedures. Chest 1977;71(5): 567–575.
14. Kim CS, Brown LK, Lewars GG, Sackner MA. Aerosol rebreathing method for assessment of airway abnormalities: theoretical analysis and validation. Am Ind Hyg Assoc J 1983;44(5):349–357.
15. Kim CS, Lewars GA, Sackner MA. Measurement of total lung aerosol deposition as an index of lung abnormality. J Appl Physiol 1988; 64(4):1527–1536.
16. Kim CS, Abraham WM, Garcia L, Sackner MA. Enhanced aerosol deposition in the lung with mild airways obstruction. Am Rev Respir Dis 1989;139(2):422–426.
17. Kim CS, Kang TC. Comparative measurement of lung deposition of inhaled fine particles in normal subjects and patients with obstructive airway disease. Am J Respir Crit Care Med 1997;155(3):899–905.
18. Kim CS, Brown LK, Lewars GG, Sackner MA. Deposition of aerosol particles and flow resistance in mathematical and experimental airway models. J Appl Physiol 1983;55(1 Pt 1):154–163.
19. Gebhart J, Heigwer G, Heyder J, Roth C, Stahlhofen W. The use of light scattering photometry in aerosol medicine. J Aerosol Med 1988; 1:89–112.
20. Heyder J, Armbruster L, Gebhart J, Grein E, Stahlhofen W. Total deposition of aerosol particles in the human respiratory tract for nose and mouth breathing. J Aerosol Sci 1975;6:311–328.
21. Lippmann M, Albert RE. The effect of particle size on the regional deposition of inhaled aerosols in the human respiratory tract. Am Ind Hyg Assoc J 1969;30(3):257–275.
22. Stahlhofen W, Rudolf G, James AJ. Intercomparison of experimental regional aerosol deposition data. J Aerosol Med 1989;2:285–307.
23. Bennett WD, Chapman WF, Lay JC, Gerrity TR. Pulmonary clearance of inhaled particles 24 to 48 hours post deposition: effect of beta-adrenergic stimulation. J Aerosol Med 1993;6(1):53–62.
24. Jaszczak RJ, Coleman RE. Single photon emission computed tomography (SPECT): principles and instrumentation (review). Invest Radiol 1985;20(9):897–910.
25. Chan HK. Use of single photon emission computed tomography in aerosol studies (review). J Aerosol Med 1993;6(1):23–36.
26. Kim CS, Hu SC, DeWitt P, Gerrity TR. Assessment of regional deposition of inhaled particles in human lungs by serial bolus delivery method. J Appl Physiol 1996;81(5):2203–2213.

27. Yu CP. Exact analysis of aerosol deposition during steady breathing. Powder Technol 1978;21:55–62.
28. Diu CK, Yu CP. Respiratory tract deposition of polydisperse aerosols in humans. Am Ind Hyg Assoc J 1983;44(1):62–65.
29. Ferron GA, Oberdörster G, Henneberg R. Estimation of deposition of aerosolized drugs in the human respiratory tract due to hygroscopic growth. J Aerosol Med 1989;2:271–284.
30. Ferron GA, Karg E, Peter JE. Estimation of deposition of polydisperse hygroscopic aerosols in the human respiratory tract. J Aerosol Sci 1993;24:655–670.
31. Heyder J, Gebhart J, Rudolf G, Schiller CF, Stahlhofen W. Deposition of particles in the human respiratory tract in the size range 0.005–15 μm. J Aerosol Sci 1986;17:811–825.
32. Bennett WD, Zeman KL, Kim C. Variability of fine particle deposition in healthy adults: effect of age and gender. Am J Respir Crit Care Med 1996;153(5):1641–1647.
33. Heyder J, Gebhart J, Rudolf G, Stahlhofen W. Physical factors determining particle deposition in the human respiratory tract. J Aerosol Sci 1980;11:505–515.
34. Hu SC, Kim CS. Deposition of fine particles in human lungs: effect of breathing pattern and gender. Proc 3rd Coll Particulate Air Pollution and Human Health 1999:11–32
35. Liu BYH, Kim CS. On the counting efficiency of condensation nuclei counters. Atm Environ 1977;11:1097–1100.
36. Stolzenburg MR, McMurry PH. An ultrafine aerosol condensation nucleus counter. Aerosol Sci Technol 1991;14:48–65.
37. Jaques PA, Kim CS. Measurement of total lung deposition of inhaled ultrafine particles in healthy men and women. Inhalation Tox (Aug 2000; in press).
38. Tu KW, Knutson EO. Total deposition of ultrafine hydrophobic and hygroscopic aerosols in the human respiratory system. Aerosol Sci Technol 1984;3:453–465.
39. Blanchard JD, Willeke K. Total deposition of ultrafine sodium chloride particles in human lungs. J Appl Physiol 1984;57(6):1850–1856.
40. Wilson FJ Jr, Hiller FC, Wilson JD, Bone RC. Quantitative deposition of ultrafine stable particles in the human respiratory tract. J Appl Physiol 1985;58(1):223–229.
41. Schiller CF, Gebhart J, Heyder J, Rudolf G, Stahlhofen W. Factors influencing total deposition of ultrafine aerosol particles in the human respiratory tract. J Aerosol Sci 1986;17:328–332.
42. Anderson PJ, Wilson JD, Hiller FC. Respiratory tract deposition of ultrafine particles in subjects with obstructive or restrictive lung disease. Chest 1990;97(5):1115–1120.
43. Wanner A, Brodnan JM, Perez J, Henke KG, Kim CS. Variability of airway responsiveness to histamine aerosol in normal subjects: role of deposition. Am Rev Respir Dis 1985;131(1):3–7.
44. Smaldone GC, Fuhrer J, Steigbigel RT, McPeck M. Factors determining pulmonary deposition of aerosolized pentamidine in patients with human immunodeficiency virus infection. Am Rev Respir Dis 1991;143(4 Pt 1):727–737.
45. Martonen TB, Katz IM. Deposition patterns of polydisperse aerosols within human lungs. J Aerosol Med 1993;6:251–274.
46. Hiller FC, Mazumder MK, Smith GM, Bone RC. Physical properties, hygroscopicity and estimated pulmonary retention of various therapeutic aerosols. Chest 1980;77(2 Suppl):318–321.
47. Kim CS, Trujillo D, Sackner MA. Size aspects of metered-dose inhaler aerosols. Am Rev Respir Dis 1985;132(1):137–142.
48. Hickey AJ, Gonda, I, Irwin WJ, Fildes FJ. Effect of hydrophobic coating on the behavior of a hygroscopic aerosol powder in an environment of controlled temperature and relative humidity. J Pharm Sci 1990;79(11):1009–1014.
49. Ferron GA. The size of soluble aerosol particles as a function of the humidity of the air: application to the human respiratory tract. J Aerosol Sci 1977;8:251–267.
50. Ferron GA, Kreyling WG, Haider B. Inhalation of salt aerosol particles- II. Growth and deposition in the human respiratory tract. J Aerosol Sci 1988;19:611–631.
51. Persons DD, Hess GD, Muller WJ, Scherer PW. Airway deposition of hygroscopic heterodispersed aerosols: results of a computer calculation. J Appl Physiol 1987;63(3):1195–1204.
52. Finlay WH, Stapleton KW. The effect of regional lung deposition of coupled heat and mass transfer between hygroscopic droplets and their surrounding phase. J Aerosol Sci 1995;26:655–670.
53. Finlay WH. Estimating the type of hygroscopic behavior exhibited by aqueous droplets. J Aerosol Med 1998;11(4):221–227.
54. Gebhart J, Heyder J, Stahlhofen W. Use of aerosols to estimate pulmonary air-space dimensions. J Appl Physiol 1981;51(2):465–476.
55. Donna E, Danta I, Kim CS, Wanner A. Relationship between deposition of and responsiveness to inhaled methacholine in normal and asymptomatic subjects. J Allergy Clin Immunol 1989;83(2):456–461.
56. Laube BL, Swift DL, Adams GK. Single-breath deposition of jet-nebulized saline aerosols. Aerosol Sci Technol 1984;3:97–102.
57. Moren F, Anderson J. Fraction of dose exhaled after administration of pressurized inhalation aerosols. Int J Pharm 1980;6:295–300.
58. Dolovich M, Ruffin R, Corr D, Newhouse MT. Clinical evaluation of a simple demand inhalation MDI aerosol delivery device. Chest 1983;84(1):36–41.
59. Newman SP, Millar AB, Lennard-Jones TR, Moren F, Clarke SW. Improvement of pressurized aerosol deposition with Nebuhaler spacer device. Thorax 1984;39(12):935–941.
60. Emmet PC, Love RG, Hannan WJ, Millar AM, Soutar, CA. The relationship between the pulmonary distribution of inhaled fine aerosols and tests of small airway function. Bull Eur Physiopathol Respir 1984;20(4):325–332.
61. Laube BL, Links JM, LaFrance ND, Wagner HN Jr, Rosenstein BJ. Homogeneity of bronchopulmonary distribution of 99mTc aerosol in normal subjects and in cystic fibrosis patients. Chest 1989;95(4):822–830.
62. Kim CS, Eldridge MA, Garcia L, Wanner A. Aerosol deposition in the lung with asymmetric airways obstruction: in vivo observation. J Appl Physiol 1989;67(6):2579–2585.
63. Smaldone CM. Deposition patterns of nebulized drugs: is the pattern important? J Aerosol Med 1994;7(Suppl 1):S25–S32.
64. Agnew JE, Pavia D, Clarke SW. Airways penetration of inhaled radioaerosol: an index to small airway function? (review) Eur J Respir Dis 1981;62(4):239–255.
65. Dolovich MB, Sanchis J, Rossman C, Newhouse MT. Aerosol penetrance: a sensitive index of peripheral airways obstruction. J Appl Physiol 1976;40(3):468–471.
66. Sanchis J, Dolovich M, Chalmers R, Newhouse M. Quantitation of regional aerosol clearance in the normal human lung. J Appl Physiol 1972;33(6):757–762.
67. Smaldone GC, Perry RJ, Bennett WD, Messina MS, Zwang J, Howite J. Interpretation of "24 hour lung retention" in studies of mucociliary clearance. J Aerosol Med 1988;1:11–20.
68. Foord N, Black A, Walsh M. Regional deposition of 2.5–7.5 μm diameter inhaled particles in healthy male non-smokers. J Aerosol Sci 1978;9:343–357.
69. Logus JW, Trajan M, Hooper HR, Lentle BC, Man SFP. Single photon emission tomography of lungs imaged with 99mTc-labeled aerosol. J Can Assoc Radiol 1984;35(2):133–138.
70. Phipps PR, Gonda I, Bailey DL, Borham P, Bautovich G, Anderson SD. Comparison of planar and tomographic gamma scintigraphy to measure the penetration index of inhaled aerosols. Am Rev Respir Dis 1989;139(6):1516–1523.

71. Perring S, Summers Q, Fleming JS, Nassim MA, Holgate ST. A new method of quantification of the pulmonary regional distribution of aerosols using combined CT and SPECT and its application to nedocromil sodium administration by metered dose inhaler. Br J Radiol 1994;67(793):46–53.
72. Fleming JS, Nassim M, Hashish AH, Bailey AG, Conway J, Holgate ST, et al. Description of pulmonary deposition of radiolabeled aerosol by airway generation using a conceptual three dimensional model of lung morphology. J Aerosol Med 1995;8:341–356.
73. Fleming JS, Halson P, Conway J, Moore E, Nassim MA, Hashish AH, et al. Three-dimensional description of pulmonary deposition of inhaled aerosol using data from multimodality imaging. J Nucl Med 1996;37(5):873–877.
74. Weibel ER. Morphology of the lung. New York: Academic Press; 1965.
75. Fleming JS, Hashish AH, Conway JH, Hartley-Davies R, Nassim MA, Guy MJ, et al. A technique for simulating radionuclide images from the aerosol deposition pattern in the airway tree. J Aerosol Med 1997;10:199–212.
76. Hashish AH, Fleming JS, Conway J, Halson P, Moore E, Williams TJ, et al. Lung deposition of particles by airway generation in healthy subjects: three dimensional radionuclide imaging and numerical model prediction. J Aerosol Sci 1998;29:205–215.
77. Hughes JMB, Brudin LH, Valind SO, Rhodes CG. Positron emission tomography in the lung (review). J Thorac Imaging 1985;1(1):79–88.
78. Rhodes CG Wollmer P, Fazio F, Jones T. Quantitative measurement of regional extravascular lung density using positron emission and transmission tomography. J Comput Assist Tomogr 1981;5(6):783–791.

Lung Models: Strengths and Limitations

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[Respir Care 2000;45(6):712–736] *Key words: airway morphology, targeted drug delivery, particle dosimetry, deposition models, aerosol.*

Introduction

Numerous clinical investigators have shown that drug efficacy and patient response are related to particle deposition patterns among lung airways.[1–18] Thus, it is possible that the efficacy of an inhaled drug would be enhanced if targeted to the appropriate region of the respiratory system. The selective distribution of an inhaled therapy could offer several advantages to aerosol therapy protocols, such as the administration of lower doses without compromising patient care and with greater cost-effectiveness. For example, if the drug could be targeted to desired sites (eg, receptors or sensitive airway cells), then adverse effects (eg, tremor, headache, dizziness, nausea, malaise) associated with therapy and perhaps overdosing, would be avoided. Similarly, if losses (drug deposition in inappropriate locations) could be minimized, the manufacturer need only load the delivery device with the appropriate amount of drug for targeted delivery, again leading to possible cost savings.

Aerosols produced by drug delivery devices (eg, metered dose inhalers [MDIs], dry powder inhalers [DPIs], and nebulizers) could be administered selectively within the respira-

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tory system, guided by mathematical models that describe the behavior and fate of inhaled particles. The models have identified the various factors affecting the motion of inhaled particles and formulated their effects on particle deposition efficiencies in airways. The development and application of mathematical models is addressed herein.

It is our intent to present mathematical models (and their associated computer codes) as being practical scientific tools worthy of being actively employed in the field of medicine. The modeling efforts described herein are considered complementary to clinical studies, rather than being abstract academic exercises. We advocate that, in the medical arena, the models be regarded as merely another technology and, in that sense, they are no different than other medical instrumentation.

A consideration of the strengths and limitations of models should account for the various factors alluded to above in both an absolute and relative sense. That is, (1) what are the strengths and limitations of models per se, and (2) what are the strengths and limitations of different models when compared? The first point is a matter of concept, the second involves technicalities. Regarding point (1), the fundamental issues are: can models be successfully integrated into the medical arena? If so, why? If not, why not? Specifically with regard to the Aerosol Consensus Conference, the seminal question seems to be: can employing models facilitate the delivery of inhaled aerosols and thereby enhance the effectiveness of drugs? The second point involves differences between models. For example, what are the scientific differences between stochastic models (eg, Hofmann and Koblinger,[19] Bergmann et al[20]) and deterministic models (eg, Yeh and Schum,[21] Martonen and Yang[22])?

In this article we shall focus on question (1). The matter of computational details (ie, question (2)) involves complex issues of a technical nature that we believe are outside the goals of this forum, and will therefore be reserved for another effort.

Methods

The deposition patterns of inhaled aerosols can be expressed in terms of three sets of parameters: the characteristics of the aerosol, the morphology of the respiratory system, and ventilatory conditions.

Aerosol Characteristics

To ascertain deposition patterns following inhalation, an aerosol must be classified in terms of the physical (and, if necessary, electrical) features of its constituent particles. A fundamental term in the field of particle technology as applied to aerosol therapy is "aerodynamic diameter." By definition, the aerodynamic diameter (D_{ae}) of a particle of arbitrary shape and density is the geometric diameter of a spherical particle of unit density that has the same Stokes terminal settling speed. For example, the D_{ae} of a droplet (eg, saline) of density ρ and geometric diameter D_g as generated by a nebulizer is $D_{ae} = (\rho)^{1/2} D_g$.

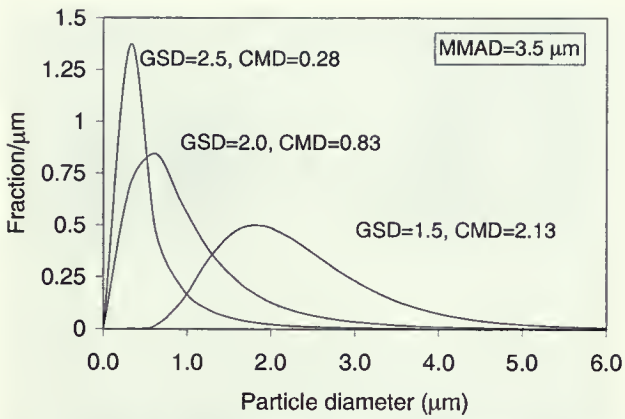

Fig. 1. Lognormal particle size distributions of representative aerosols. The mass median aerodynamic diameters (MMADs), count median diameters (CMDs), and geometric standard deviations (GSDs) are noted.

In a given case, the size distribution of the administered aerosol may be of primary interest. There are many commercial instruments available to measure size distributions. Regarding medical devices, the outputs of MDIs, DPIs, and nebulizers are most commonly measured using cascade impactors and impingers, depending on the size resolution desired. Cascade impactors are employed to provide high-resolution particle size classification, yielding information about the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the particle size distribution.

Figure 1 illustrates the particle size distributions corresponding to typical aerosols produced by commonly-used MDIs, DPIs, and nebulizers. The representative polydisperse aerosols assume a log-normal particle size distribution and have an MMAD value of 3.5 μm but different GSD (σ_g) and count median diameter (CMD) values. These parameters are related through the Hatch-Choate conversion equation:

$$\text{MMAD} = \text{CMD} \times \exp(3\ln^2\sigma_g)$$

An important point, clearly illustrated in Figure 1 but frequently overlooked in aerosol delivery protocols, is that a sizeable *number* of the constituent particles are of submicron size.

Lung Morphology

To describe the geometry of the lung, comprehensive anatomical data are needed. The features that must be

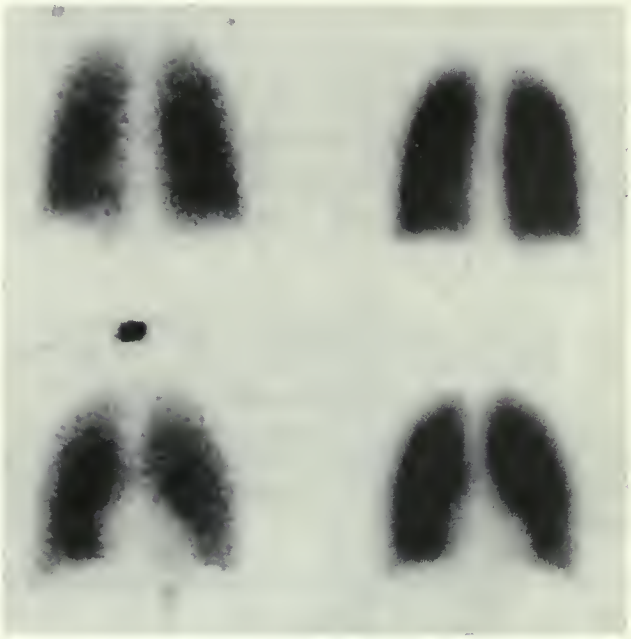

Fig. 2. Lung images used in defining the outer lung boundary. Upper left: posterior ventilation scan. Upper right: posterior perfusion scan. Lower left: anterior ventilation scan. Lower right: anterior perfusion scan.

documented include the gross structure and details of its components. For example, regarding structure, the spatial orientation of the branching network (bifurcation angles, gravity angles), the composition of the network by physical location (tracheobronchial, pulmonary) and airway function (smooth muscle, alveolated) must be known. Regarding individual airways, they must be described by their dimensions (lengths, diameters), shapes (straight, curved), and nature (smooth-walled, rough).

The lung morphology employed herein is physiologically realistic. As detailed in the next two sections, its overall branching structure is based on laboratory data from planar gamma camera and single photon emission computed tomography (SPECT) studies. Internal surfaces of airways are based on fiberoptic bronchoscopy examinations.

Branching Structure. Our anatomical model of the human lung is a hybrid based on morphometric data from the literature and direct clinical observations. The key references employed in determining an asymmetric lung geometry were Horsfield and Cumming,[23] Horsfield et al,[24] and Horsfield,[25] and the irregular Model B of Weibel.[26,27]

The morphology was first presented by Martonen et al.[28] In that work, the computer-generated morphology was designed using information from planar gamma camera images (Fig. 2). In Figure 3 the outer boundary of the image is defined and divided into its central (C), intermediate (I), and pulmonary (P) airways. The morphological

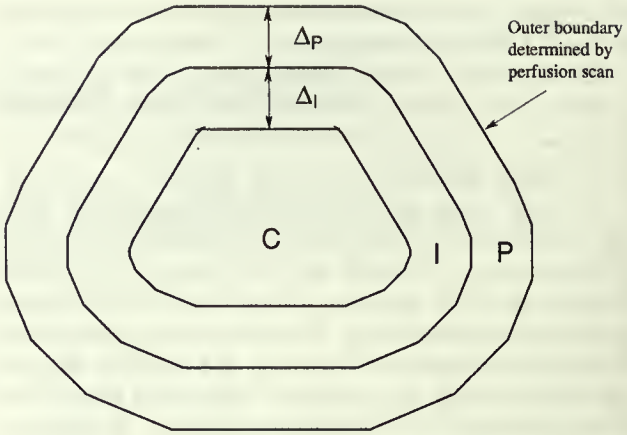

Fig. 3. Application of the computer algorithm describing human lung morphology. The template of the computer code is based on the outer lung boundary determined in the medical arena (see Fig. 2). (From Reference 29, with permission.)

Table 1. Airway Composition of Scintigraphy Data: Central, Intermediate, and Peripheral Zones

Lung Generation	Partition of Scan		
	Region C	Region I	Region P
1	0	2	0
2	4	0	0
3	4	4	0
4	8	8	0
5	16	16	0
6	32	32	0
7	22	62	44
8	24	118	114
9	34	244	234
10	60	485	479
11	102	606	1,340
12	182	896	3,018
13	326	1,528	6,338
14	542	2,897	12,945
15	846	5,637	26,285
16	1,484	10,977	53,075
17	2,763	21,700	106,609
18	5,574	42,464	214,106
19	11,038	83,810	429,440
20	21,953	165,798	860,825
21	44,156	329,152	1,723,844
22	88,665	654,410	3,451,229
23	178,436	1,301,820	6,908,352

C = central zone
I = intermediate zone
P = peripheral zone
(From Reference 29, with permission.)

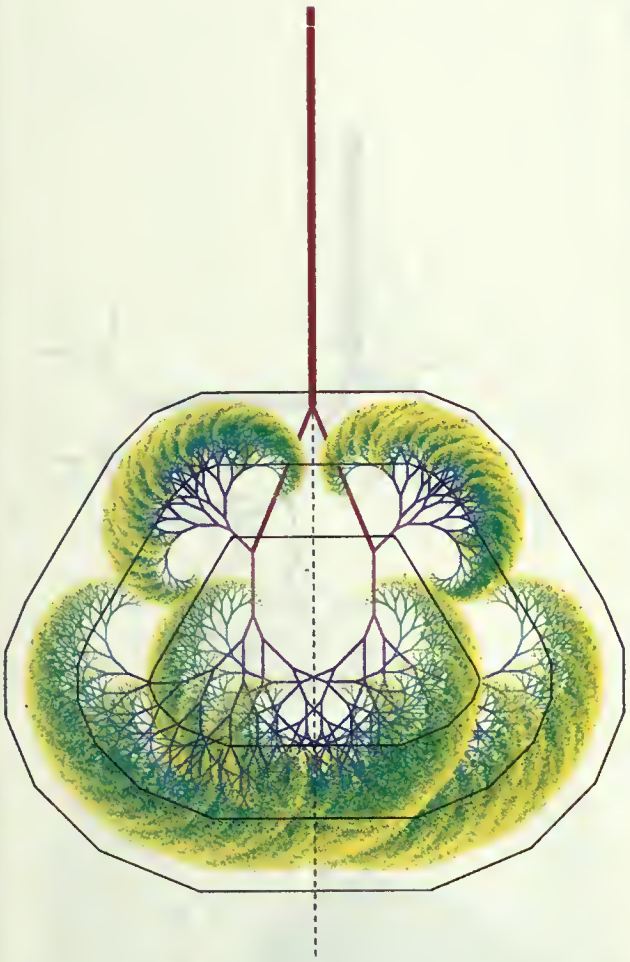

Fig. 4. A computer-generated physiologically realistic lung morphology. (From Reference 29, with permission.)

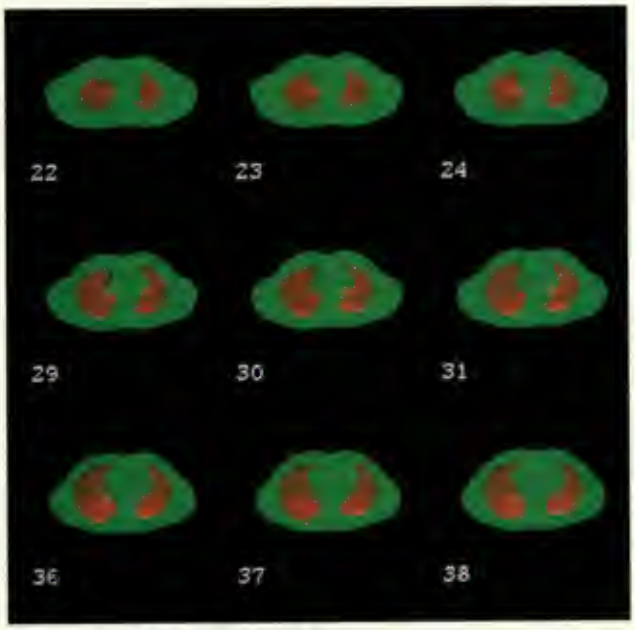

Fig. 5. A typical example of the three-dimensional distribution of aerosol from a nebulizer (in red) overlaid on the corresponding aligned magnetic resonance images segmented into lung, soft tissue, and bone (in green). The images are transverse cuts through the thorax with the front of the subject uppermost and the left side of the subject on the right of the images (ie, as viewed from the feet with the subject supine). The images start with the apex of the lung top left and proceed down the lung, running left to right then top to bottom.

algorithm has evolved so that in clinical practice it can now be customized to each patient on an individual basis (Fig. 4), as outlined in Martonen et al.[29] For demonstration purposes, an itemization of the airway-by-airway composition of scintigraphy data, as determined by the morphological computer algorithm, is given in Table 1.

The morphology computer code may also be employed for the analysis of SPECT data from human subject tests (Fig. 5). In that sequence of images, the apex of the lung is at the top left position. The transverse sections proceed left to right, row by row. Aligned magnetic resonance was used to determine the outline of the right lung, which allowed aerosol deposition patterns to be related to morphological sites. Figure 6 shows angular views of the tracheobronchial network. The branching network changes markedly with progression from branches $0 \leq I \leq 4, 8, 12, 16$. This information is given simply to demonstrate to those not involved in modeling that the tracheobronchial morphology quickly becomes very complex. Figure 7 shows analogous transaxial views.

In Figure 8, the voxel matrix used in SPECT regimens is superimposed on a three-dimensional lung morphology. Figure 9 shows an itemization of the total number of individual airways in each voxel of a transverse section of human lungs. For an even greater resolution, that number (ie, total) in a given voxel can be further reduced into the number of each type of airway (see Table 2). For more detailed information, we refer the interested reader to the series of Martonen et al.[30–33]

In Figure 10 we present preliminary results of an original software program still in development. It represents our intent to be ever more anatomically correct. A salient feature of the three-dimensional branching structure is that the individual airways are depicted as tubular structures (ie, not only as centerlines, which is a widespread practice in the modeling field). The disadvantage of using only centerlines to specify airway positions is that when real diameters are added, the generated airway volumes may intersect (ie, overlap in space), which would be an aphysical situation. Therefore, by plotting three-dimensional tubular airways we may *a priori* avoid such situations when constructing computer algorithms describing in vivo con-

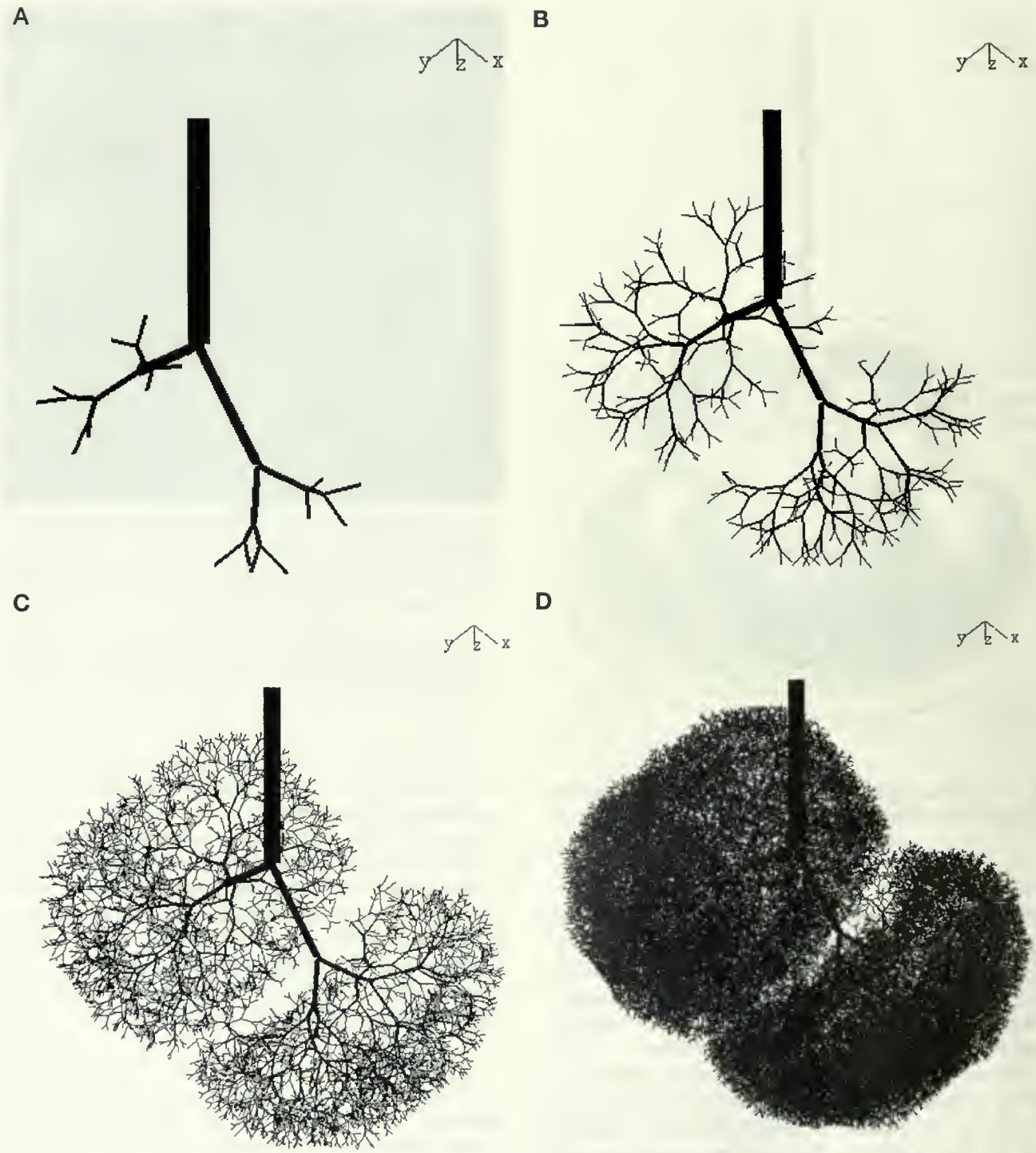

Fig. 6. Angular views of the human tracheobronchial compartment as the number of generations (l) increases: A: $0 \leq l \leq 4$. B: $0 \leq l \leq 8$. C: $0 \leq l \leq 12$. D: $0 \leq l \leq 16$.

ditions. We are in the process of improving the current software by, for example, smoothing the abrupt sites of transition at airway junctures.

Figure 11 shows a computer-generated image, based on SPECT data, of the left and right lungs of the human respiratory system. This imaging protocol is also a work-in-progress. The respective lung images will be produced by allowing the branching network illustrated in Figure 10 to be extended to completion at the level of individual alveoli. Those termination points (ie, alveoli) then will be

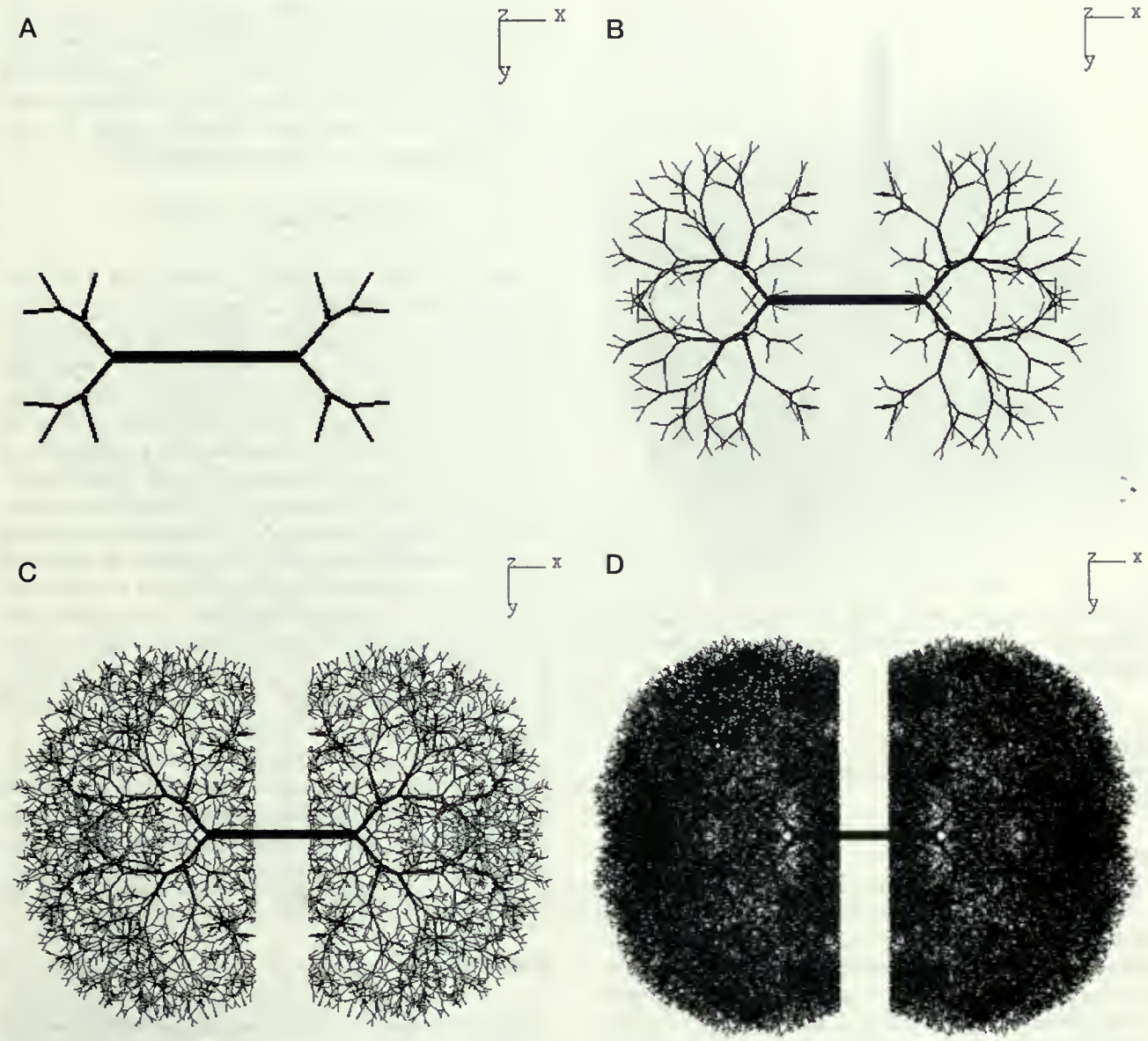

Fig. 7. Top views of the human tracheobronchial compartment as the number of generations (l) increases: A: $0 \leq l \leq 4$. B: $0 \leq l \leq 8$. C: $0 \leq l \leq 12$. D: $0 \leq l \leq 16$.

graphically connected with inclusive incremental areas to match the two three-dimensional bounding surfaces shown in Figure 11. In this way, the morphology can be customized to SPECT data from each patient.

Individual Airways. Figure 12 shows two views of the upper bronchi taken during a routine fiberoptic bronchoscopy examination. The panels clearly show the existence of cartilaginous rings, natural structural features of normal human airways. For accurate modeling, such surface elements must be integrated into morphological descriptions of human lungs. Yet, there is only one dosimetry model in the published literature that accounts for real lung surfaces and carinal ridge shapes.[34–38] As will be detailed later, such surface structures can have pronounced effects on air motion and, therefore, on the behavior of inhaled drug particles. It is imperative that lung surfaces be realistically simulated so that the dose delivered to patients with airway diseases can be accurately determined, particularly when localized doses, or hot spots of deposition, are common.

In Figure 13 (A and B) two additional lobar views within the normal tracheobronchial tree further show the shapes of carinal ridges within bifurcation zones and the complex

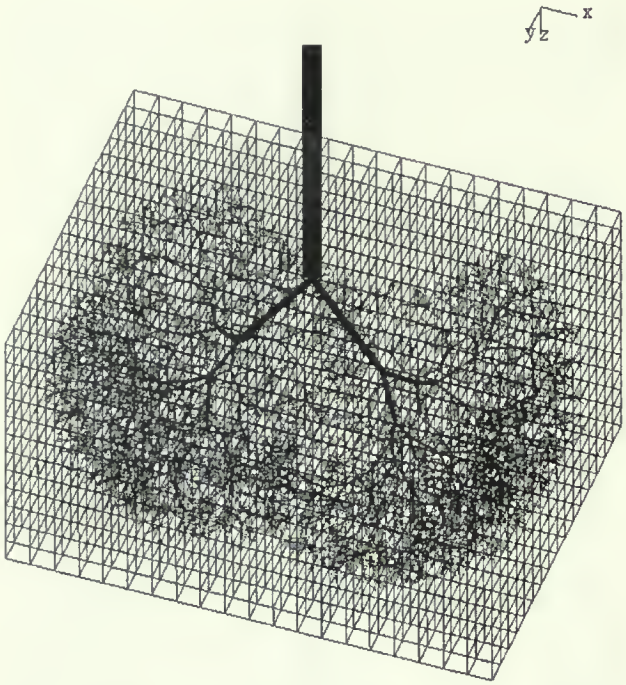

Fig. 8. Superposition of the single photon emission computed tomography voxel matrix with the computer-generated three-dimensional lung morphology.

branching structure of the airway network structures, which must be included in the development of accurate lung dosimetry models.

Ventilation

The breathing pattern used while inhaling an aerosolized drug is a critical factor affecting the dispersion of aerosol among airways. In aerosol therapy practice, it has been most common to utilize spontaneous breathing protocols wherein patients breathe in their usual (ie, natural) fashion. Such a natural breathing pattern could then be modified if the patient was advised to breathe in another mode, such as "slow and deep." The key variables are: tidal volume (V_T, in mL) and time of inspiration (in seconds). Table 3 shows the representative components of ventilation as a function of age and activity level.[39]

For modeling purposes, it may be advantageous to actively regulate breathing conditions, using, for example, the academic breathing regimen employed in laboratory inhalation exposure tests.[40,41] In those experiments the subjects were trained to breathe using a constant inspiratory flow. Findings also suggest that regulating the time of breath-holding is also a critical element[42] affecting the efficiency and site of aerosol deposition. The components of ventilation can be translated into terms more useful in engineering parlance. For instance, the V_T (in cm^3) and breathing frequency (f, in breaths/min) values of use in respiratory physiology studies can be used to determine the inspiratory flow rate (Q, L/min). If the time of inspiration is denoted as T_{in} (s), then $Q = V_T/T_{in}$ and the *mean* fluid velocity (v, in cm/s) in an airway can be expressed as v = Q/[cross-sectional area]. When the airway is a cylinder of diameter d, we have $v = Q/[\pi d^2/4]$.

Aerosol Deposition Model

Martonen[43] has developed a mathematical model describing particle deposition in the human respiratory system, developed especially for applications in aerosolized drug delivery protocols. A systematic series of studies examined the effects of ventilatory variables,[42] aerosol characteristics,[44] and lung morphology.[45] In those studies, the model was validated by comprehensive comparisons of predicted particle deposition patterns with data from human subject inhalation exposures. That model has continued to evolve (eg, Martonen and Yang[22]) with improved technical simulations including, for example, the inclusion of developing (transient) flow conditions in airways[46] and formulations of the effects of airway surface structures (cartilaginous rings) on particle motion.[37,38] In the evolution of the model, primary emphasis has been on making it ever more physiologically realistic. Some of the salient features of the model are outlined below.

In the development of aerosol deposition models, particle motion has been simulated under the action of certain external forces. The deposition efficiencies have been calculated assuming that the forces were independent. Interactive effects were subsequently accounted for by superposition, as detailed below.

Particle Physics

Figure 14 illustrates the dominant particle deposition mechanisms in human airways: inertial impaction, sedimentation, and diffusion.

Inertial Impaction. The momentum of a drug particle is the product of its mass and velocity. When a particle has sufficient momentum, its trajectory will deviate from that of a corresponding fluid particle (ie, a particle having the physical properties, density, and viscosity of the fluid). At an airway branching site, a centrifugal force field is created by motion in the curved passageway, which causes the particle to impact the outer (ie, directed away from the radius of curvature) surface of the airway. Accordingly, this deposition mechanism is termed *inertial impaction*. For a particle of given mass, this mechanism is most efficient where velocities are high; namely, the upper airways of the tracheobronchial tree (Fig. 15). The process of inertial impaction has been formulated by numerous au-

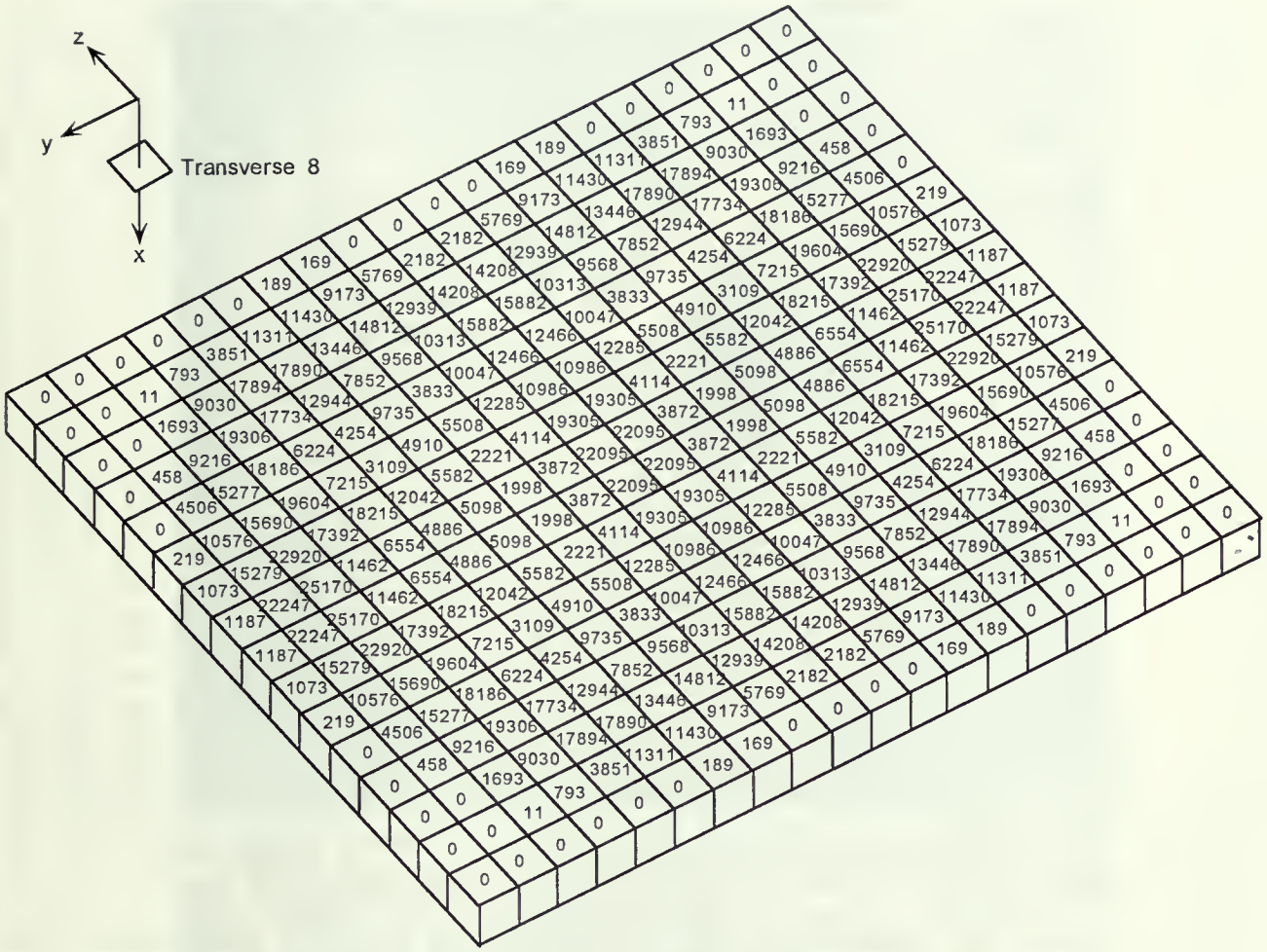

Fig. 9. A transverse section of single photon emission computed tomography data (see coordinate axes for position). In each voxel the number of individual airways is itemized. Related information is given in Table 2.

thors assuming different conditions (eg, velocity fields). The particle deposition efficiency equations most commonly used for lung deposition computations are Landahl and Herrmann,[47] Beeckmans,[48] Cheng and Wang,[49] Yeh,[50] Crane and Evans,[51] and Martonen.[52]

Sedimentation. This mechanism describes particle deposition under the action of gravity. It is, therefore, a function of residence time (ie, the time that a particle spends in an airway), which may be written as T (s) = L (cm)/v (cm/s), where L is the length of an airway and v is the mean velocity. For a particle of given mass, this mechanism is most efficient where velocities are low, namely, the peripheral airways of the tracheobronchial tree and, especially, the pulmonary compartment (see Fig. 15) inclusive of generations 16–23. Figures 15B and 15C show the increase in velocity with increasing exercise that would act to promote deposition. The efficiency with which gravity deposits particles in airways has also been described by various authors using different assumptions; the equations most frequently used are those by Landahl,[53] Beeckmans,[48] Wang,[54] and Martonen.[52]

Diffusion. The random Brownian motion of particles can also result in their contact with airway surfaces. As with sedimentation, this mechanism is also a function of the residence time; that is, deposition by diffusion is most efficient in regions of the lung where velocities are lowest. The most popular equations used to describe particle deposition in lungs by diffusion are those of Ingham[55–57] and Martonen.[43,52] The latter's work has evolved to account for developing flows and surface features (eg, cartilaginous rings and carinal ridge shapes) of airways.[37,38]

Other deposition mechanisms that can affect particle deposition in human airways are: electric charge effects, interception, and cloud settling. These processes are depicted in Figure 16. In the research environment, great efforts are made to minimize the effects of these processes during inhalation exposures. That is, these deposition processes are studiously avoided. For instance, it has become

Table 2. Airway Composition of SPECT Voxels in Row 8 of Coronal Layer 8*

Generation	Voxel																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0
7	0	0	0	0	2	1	0	0	0	0	0	0	0	0	1	2	0	0	0	0
8	0	0	0	1	3	0	0	0	0	0	0	0	0	0	0	3	1	0	0	0
9	0	0	0	4	2	0	0	1	0	0	0	0	1	0	0	2	4	0	0	0
10	0	0	0	4	4	0	0	0	0	0	0	0	0	0	0	4	4	0	0	0
11	0	0	5	10	4	0	0	0	0	0	0	0	0	0	0	4	10	5	0	0
12	0	0	16	9	2	0	0	0	0	0	0	0	0	0	0	2	9	16	0	0
13	0	2	30	14	4	0	2	0	1	4	4	1	0	2	0	4	14	30	2	0
14	0	6	55	24	10	0	4	0	2	16	16	2	0	4	0	10	24	55	6	0
15	0	37	85	29	22	3	10	0	4	41	41	4	0	10	3	22	29	85	37	0
16	0	77	152	47	33	13	23	0	12	83	83	12	0	23	13	33	47	152	77	0
17	0	171	262	91	65	31	49	0	34	160	160	34	0	49	31	65	91	262	171	0
18	0	363	476	174	111	59	96	6	73	332	332	73	6	96	59	111	174	476	363	0
19	7	722	876	355	209	131	184	36	129	692	692	129	36	184	131	209	355	876	722	7
20	38	1433	1686	705	424	265	344	102	237	1427	1427	237	102	344	265	424	705	1686	1433	38
21	128	2816	3229	1419	808	601	661	234	469	2828	2828	469	234	661	601	808	1419	3229	2816	128
22	311	5594	6205	2855	1616	1240	1262	524	966	5533	5533	966	524	1262	1240	1616	2855	6205	5594	311
23	703	11026	12093	5721	3235	2542	2463	1094	1945	10979	10979	1945	1094	2463	2542	3235	5721	12093	11026	703
Total number of airways	1187	22247	25170	11462	6554	4886	5098	1998	3872	22095	22095	3872	1998	5098	4886	6554	11462	25170	22247	1187

SPECT = single photon emission computed tomography
*See Figure 9.

standard laboratory practice to rigorously control electric charge effects by using a variety of devices and laboratory techniques[40,58–63] to ensure that the sampled aerosol has a Boltzmann equilibrium electric charge distribution when inhaled by human subjects. However, in the medical arena, aerosol therapy protocols on either an inpatient or outpatient basis are not controlled in an analogous fashion regarding electric charge effects. Therefore, in the delivery of medicinal aerosols from MDIs, DPIs, or nebulizers, electric charge effects on deposition should not be ignored *a priori*.

Electric Charge Effects. The role of forces derived from electric charges on the deposition of inhaled particles has not been extensively studied and is not well understood. This is somewhat surprising since an increase in the deposition of therapeutic aerosol particles as a consequence of electric charge effects was noted more than 50 years ago by Wilson.[64] There is more recent theoretical and experimental evidence that likewise indicates that electric charges can under certain conditions affect aerosol deposition. For example, the influence of electric charges have been described mathematically by Chan and Yu,[65] and the effects on deposition have been measured in particle deposition studies with human subjects[66,67] and with replica casts of human airways.[68,69]

Because of the potential importance of electric charge effects in aerosol therapy practice, we shall comment briefly on certain technical issues affecting particle deposition in tubes *per se*, be they airways or components of delivery systems (eg, spacers). There are two fundamental factors involved in the consideration of electric charge effects. The first factor is the image force. This is a single particle effect and involves an interaction between the inhaled particle and the surrounding surface. This process is depicted in Figure 16. The second factor is the space charge force. This depends on the aerosol concentration and involves the mutual repulsion of particles that may be, in turn, directed toward the bounding walls. The available theoretical and experimental information, though limited, seems to suggest that for typical inhalation exposures of therapeutic aerosols, image forces are stronger than space charge

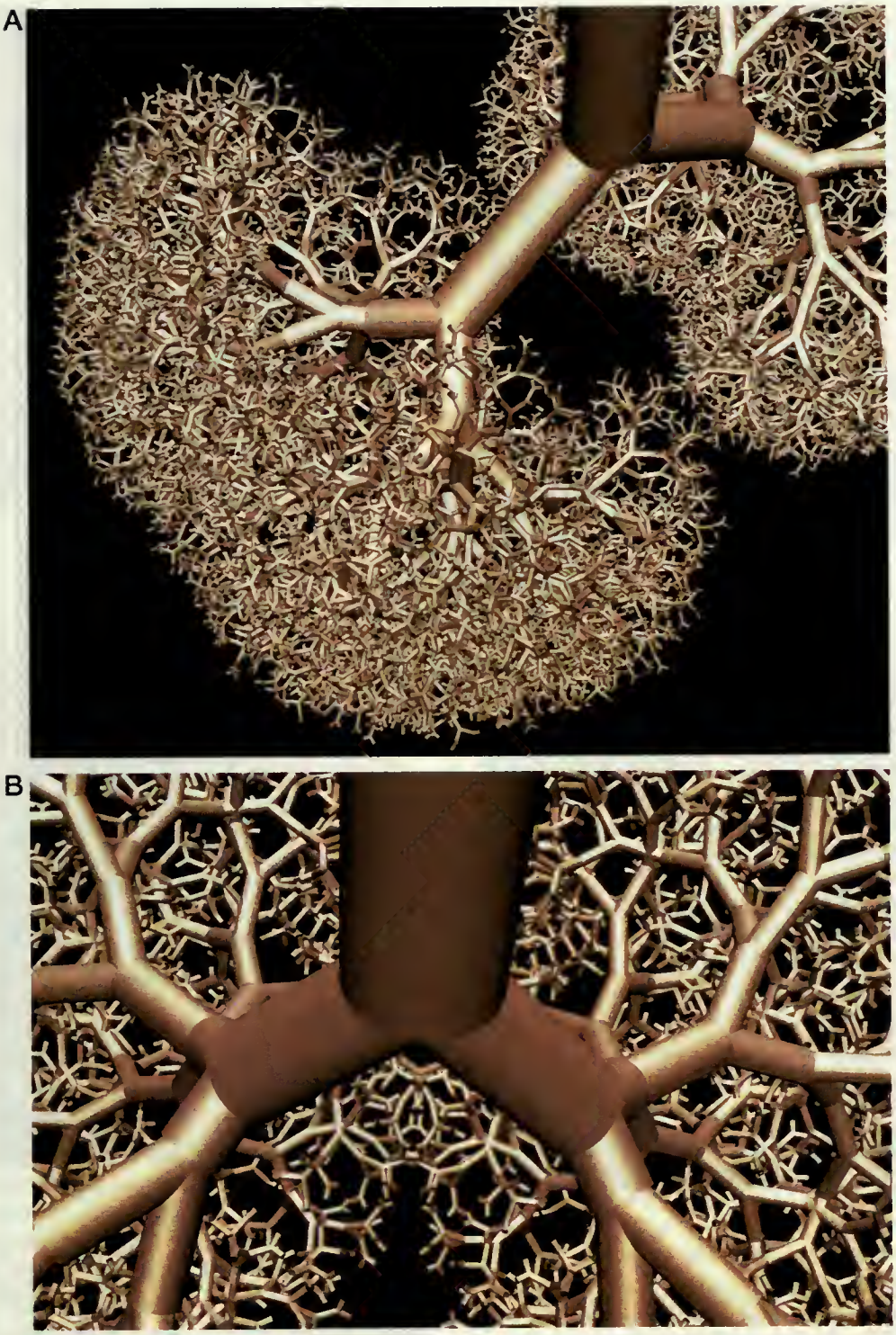

Fig. 10. Results of a new graphical procedure to simulate three-dimensional airways. For clarity, only 14 levels of branching in the tracheobronchial tree are shown: A: Overview, with the trachea and main bronchi in the upper right-hand corner. B: Detailed view of the three-dimensional network, beginning at the level of the right main bronchus.

Fig. 11. Computer-generated three-dimensional view of human lungs. The display is consistent with the results of our scintigraphy work with human subjects (see Figs. 2 and 5).

forces and will have more of an effect on the airborne behavior and deposition of inhaled particles.

Interception. Deposition by interception takes place when the center of mass of a particle remains on the fluid path transporting it but the particle still comes into contact with a bounding wall. Interception is an effective deposition mechanism for particles having elongated shapes, such as fibers. The potential importance of fiber-shaped particles in aerosol therapy was recognized by Gonda and Khalik,[70] Chan and Gonda,[71] and Johnson and Martonen.[72] A salient feature of a fiber's geometry regarding inhalation is that its aerodynamic diameter is $D_{ae} = Kd\ (l/d)^{0.0116}$ where K is a material constant (equal to 2.19 for asbestos) and l and d are the length and diameter of the fiber, respectively. The key point is that D_{ae} is relatively independent of length. That data suggests that a fiber has inherent features that are highly desirable in a drug delivery vehicle. That is, if a drug could be packed into a hollow fiber, the dosage could be increased by simply increasing fiber length, which could be done without affecting the fiber's aerodynamic size. In that scenario, more drug could be delivered more efficiently to a prescribed lung location to treat a disease. As a direct result, the efficacy of the drug could be enhanced by controlling particle characteristics (fiber length).

Despite the clear advantages to be gained by using rod-shaped particles as drug carriers, the use of fibers seemed to be only a fanciful notion because there was no known way to produce such aerosols. That has now changed. Johnson et al[73] have developed a method to generate lipid microtubule aerosols. An individual microtubule is a straight, hollow, tubular structure of circular cross-section and consists of a helically-wound lipid bilayer membrane. In the cited manuscript, the geometric lengths and diameters of representative microtubules were in the 8–12 μm and 0.5–0.7 μm range, respectively. Moreover, Johnson et al[73] demonstrated that the hollow microtubules can encapsulate drugs, and have the necessary physical and aerodynamic properties to be integrated into targeted drug delivery regimens.

Cloud Settling. The phenomenon of cloud settling has been discussed by Fuchs,[74] and the conditions necessary for it to occur were formulated in general terms. The fundamental premise is that if the particle mass concentration in an aerosol is sufficient, then an array (or, "cloud") of particles may behave as an entity. Regarding the inhalation

[A]

[B]

Fig. 12. Views within human tracheobronchial airways taken during fiberoptic bronchoscopy. A: Cartilaginous rings in the trachea. B: Cartilaginous rings in the main bronchi distal to the carinal ridge. (From Strausz J, Papai Z, and Szima B. Bronchoscopic aspects of human lung diseases. Koranyi National Institute of Pulmonology, Budapest. *http://korb1.sote.hu/broncho/album/album000.htm*, 1996, with permission.)

[A]

[B]

Fig. 13. Views within human lungs taken during fiberoptic bronchoscopy. A: Branching sites (trifurcation) in the right upper lobe. B: Airway divisions at the left upper lobe. (From Strausz J, Papai Z, and Szima B. Bronchoscopic aspects of human lung diseases. Koranyi National Institute of Pulmonology, Budapest. *http://korb1.sote.hu/broncho/album/album000.htm*, 1996, with permission.)

Table 3. Ventilation in Human Subjects as a Function of Age and Activity Level

Age (mo)	Sedentary			Light			Heavy		
	f (breaths/min)	V_T (mL)	V_E (mL)	f (breaths/min)	V_T (mL)	V_E (mL)	f (breaths/min)	V_T (mL)	V_E (mL)
7	35	42	1,470	32.0	187	5,984.0	81.1	222	18,004.2
22	28	84	2,352	36.9	222	8,191.8	79.9	308	24,609.2
48	22	152	3,344	37.3	289	10,779.7	70.4	460	32,384.0
98	18	266	4,788	28.4	494	14,029.6	46.5	903	41,989.5
360	14	500	7,000	15.5	1,291	20,010.5	24.5	2,449	60,000.5

f = respiratory rate
V_T = tidal volume
V_E = minute volume ($V_T \times f$)

of an aerosol, the cloud would have its own aerodynamic characteristics; that is, the individual particles will be masked. The constituent particles will not behave according to their individual aerodynamics properties, but rather will be an element of the cloud *per se* (see Fig. 16). As discussed in the next paragraph, the cloud settling phenomenon is not an abstract notion and may actually prove to be of practical value in drug delivery protocols.

The occurrence of cloud settling has been experimentally detected for cigarette smoke by Martonen et al[75] and Martonen.[76] In those tests, highly concentrated deposits of smoke particles were observed within airway bifurcations of casts of the human upper tracheobronchial tree, especially at carinal ridges. The deposits were not consistent with the known submicron size of cigarette smoke (MMAD = 0.4 μm, GSD = 1.45). However, the sites were related to the distributions of bronchial carcinomas in human subjects. To explain the results, Martonen[76] developed a theory describing the onset of cloud settling within human lungs. Cloud settling may take place when the particle mass concentration of an inhaled aerosol exceeds a value of about 5×10^{-8} g/cm^3. Martonen[76] showed that cigarette smoke had the necessary mass concentration (about 10^{-4} g/cm^3) to be susceptible to this phenomenon.

A straightforward response to the aforementioned experimental and theoretical findings would be to integrate those results into the administration of inhaled drugs. That is, it would seem that particle mass concentration would be a critical parameter to regulate so that, for example, an inhaled drug would experience cloud settling and could be targeted to appropriate sites. A logical question would seem to be: if lung cancer were to be treated by an inhaled drug (aerosol chemotherapy), why not construct a device capable of generating an aerosol with the same aerodynamic properties as the agent (ie, cigarette smoke) that produced the disease?

Critical variables in the aforementioned deposition probability formulas are the nature of the motion (eg, laminar, turbulent) and the magnitude of the fluid (ie, air) velocity. This is so because the inhaled drug particles are entrained and transported by air streams. Therefore, this subject will be addressed in the following section.

Fluid Dynamics

In the most commonly used particle deposition models, idealized fluid dynamic conditions are assumed. For reference, Figure 17 shows fluid motion in a tube. Fluid enters the tube with a uniform (flat) velocity profile. With progression through the tube, the velocity profile becomes fully developed and is transformed into a parabolic profile. The length, L_{FD}, necessary for flow to become fully developed in a tube of diameter d can be expressed as $L_{FD}/d = 0.06$ Re, where $Re = dv\mu/\rho$, and V, μ, and ρ are the mean fluid velocity, absolute fluid viscosity, and fluid density, respectively.[77] The results of Zhang and Martonen[78,79] suggest that most tubular airways in human lungs are not of sufficient lengths for flows to become fully developed. Those findings suggest that velocity profiles are most likely to have intermediate forms corresponding to the transition between uniform and parabolic profiles exhibited in Figure 17. The situation is made even more complicated by airway branching. The experimental findings of Schroter and Sudlow,[80] Olson et al,[81] Sudlow et al,[82] Olson et al,[83] Chang and El Masry,[84] and Isabey and Chang[85] suggest that the air streams immediately downstream from bifurcations have skewed profiles induced by the curved motion. These complex flow patterns have made it necessary to assume idealized flow patterns in order to develop particle dosimetry models.

With regard to fluid dynamics in the lung, the subject of lung dosimetry modeling is currently in a state of great flux. The availability of computational fluid dynamics software has transformed modeling both in scope (ie, the number of people engaged in modeling) and sophistication (ie, the complexity of the scientific issues addressed). The third-party, commercially-available packages may employ different numerical analysis techniques to solve the Navier-

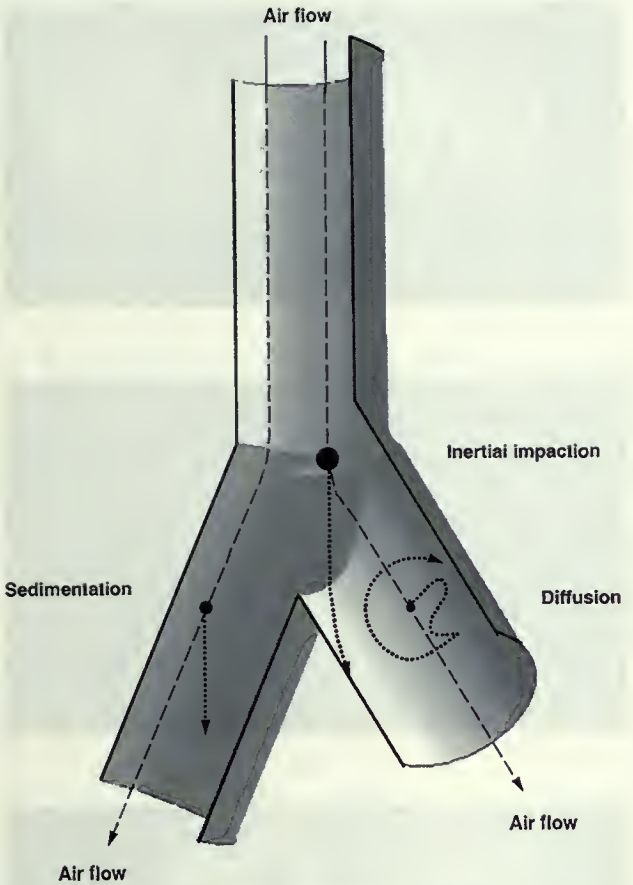

Fig. 14. Particle deposition mechanisms at an airway branching site: inertial impaction, sedimentation, and diffusion.

Stokes equations describing fluid motion. For example, to solve the system of equations, the code CFX-F3D (AEA Technology, Harwell, United Kingdom) uses the finite volume method, whereas FIDAP (Fluent Inc, Lebanon, New Hampshire, United States) uses the finite element method. In the text below, examples are provided that demonstrate the versatility of such codes and their potential positive influence on aerosol therapy protocols.

Let us now refer to the cartilaginous rings presented in the fiberoptic bronchoscopy illustrations (see Fig. 12). Figures 18A, 18B, and 18C show a computer simulation of such cartilaginous rings lining a human bronchus. Figure 19 shows the velocity field in the bronchus. The effects of the rings are pronounced, as determined using the software code FIDAP. There are three distinct features of the motion. First, a core flow is produced in the airway lumen that is quite different from the motion in a smooth-walled tube.[46] Second, there is a buffer zone adjacent to the rings (ie, intermediate to the rings and core), which, depending on ventilatory variables, may contain fluid instabilities. Finally, there are highly localized currents (or eddies) between the cartilaginous rings, as shown in Figure 20. A systematic study of the effects of rings was performed by

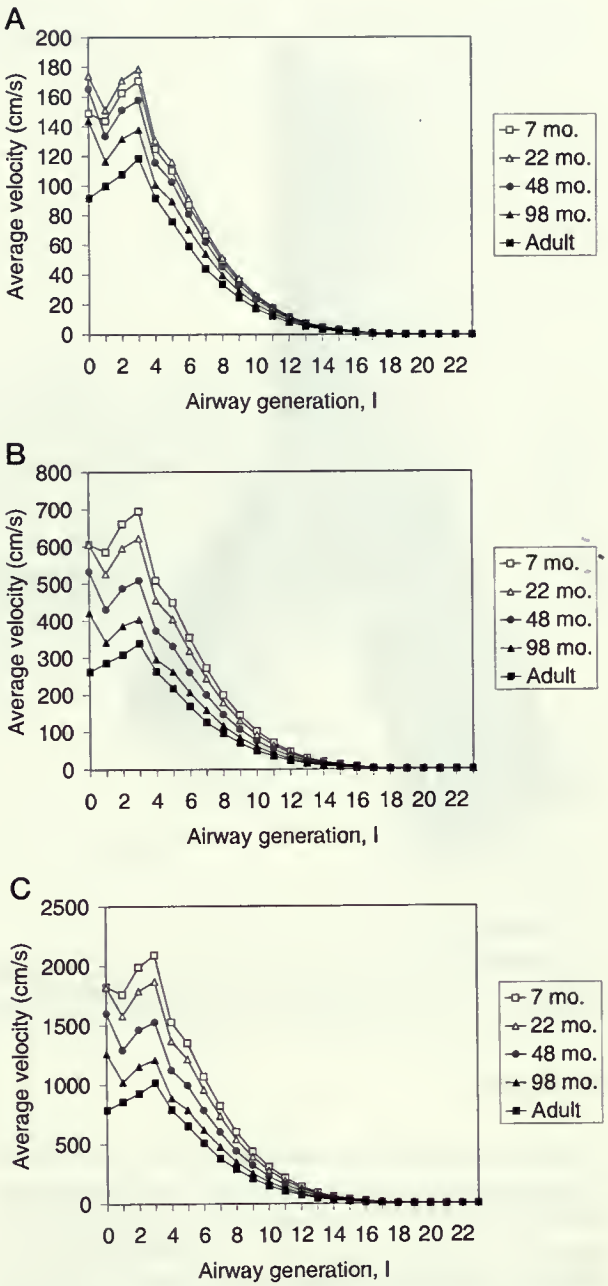

Fig. 15. Air stream velocities within human lungs. The data are presented as a function of subject age for applications to pediatric medicine (addressed later in the text). A: Sedentary. B: Light activity. C: Heavy activity. See Table 3 for related material.

Musante and Martonen.[86] The findings suggest that such eddies may trap small particles ($D_g < 0.5\ \mu m$) that would circulate until their deposition to airway walls is enhanced because of the action of diffusion. Thus, the effects of airway surfaces may be highly localized or may be propagated downstream. In the latter case, the effects of flow disturbances produced at rings (for example) may affect particle deposition in distal regions.

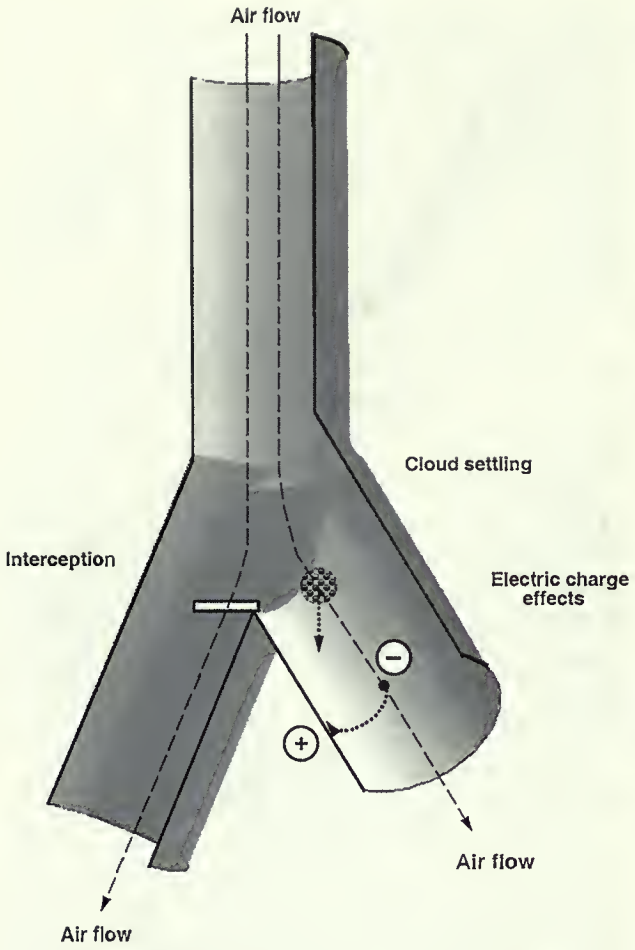

Fig. 16. Particle deposition mechanisms at an airway branching site: electric charge effects, interception, and cloud settling.

Aerosol Motion

A self-consistent set of particle deposition equations for the aforementioned deposition processes was presented by Martonen.[52] That is to say, identical assumptions were employed in the derivation of the respective formulas. This is a major difference between the model proposed by Martonen[43] and other models presented in the literature (eg, Yeh and Schum,[21] Yu and Diu,[87] Egan and Nixon,[88] Phalen et al,[89] and Anjilvel and Asgharian[90]). Those modelers used inconsistent sets of particle deposition formulas.

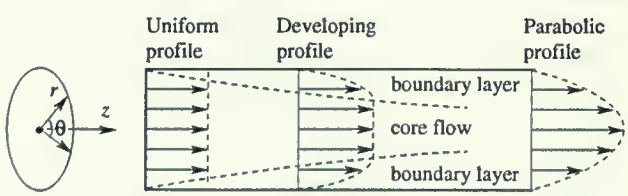

Fig. 17. Idealized fluid motion in a cylinder simulating an airway.

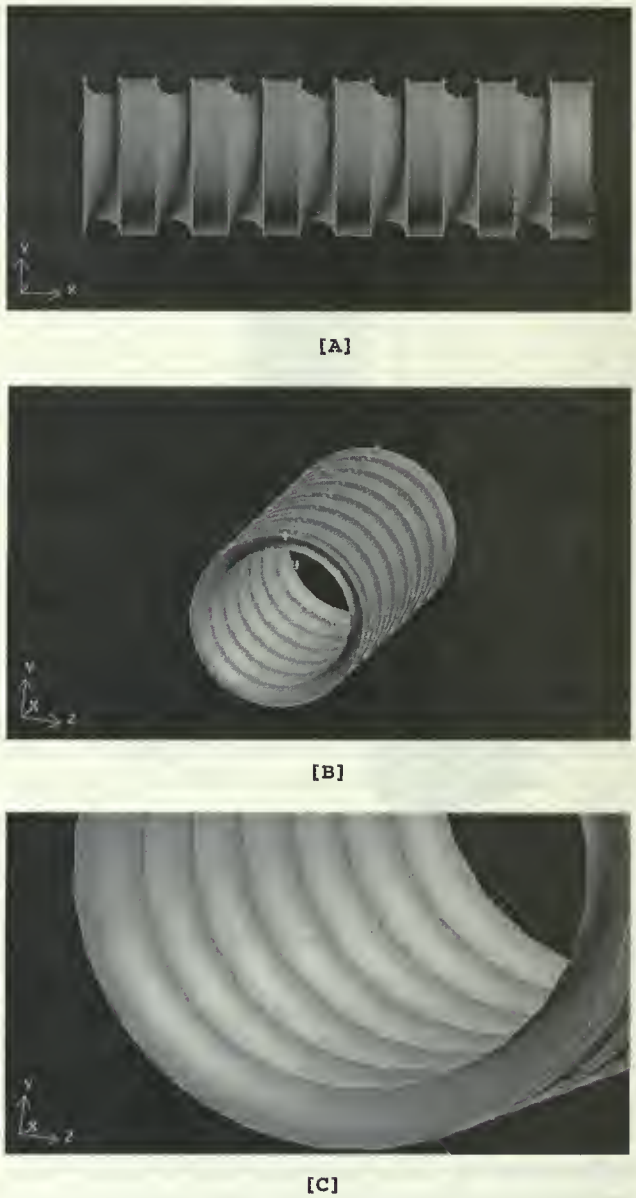

Fig. 18. Computer graphic describing a cartilaginous ring-lined human bronchus. A: Side view. B: Angular perspective. C: Details of the rings.

That is, they employed different equations derived by different authors for different conditions. For example, the inertial impaction formulas from the works of either Findeisen[91] or Landahl and Herrmann,[47] the sedimentation formulas from either Landahl[53] or Beeckmans,[48] and the diffusion formulas from either Gormley and Kennedy[92] or Ingham[55] have been used in single models. The problem is that although the individual formulas may be suitable, they do not fit together as a system; specifically, they were based on different fluid flow conditions. Hence, at a given site within the lung, the aforementioned modelers may

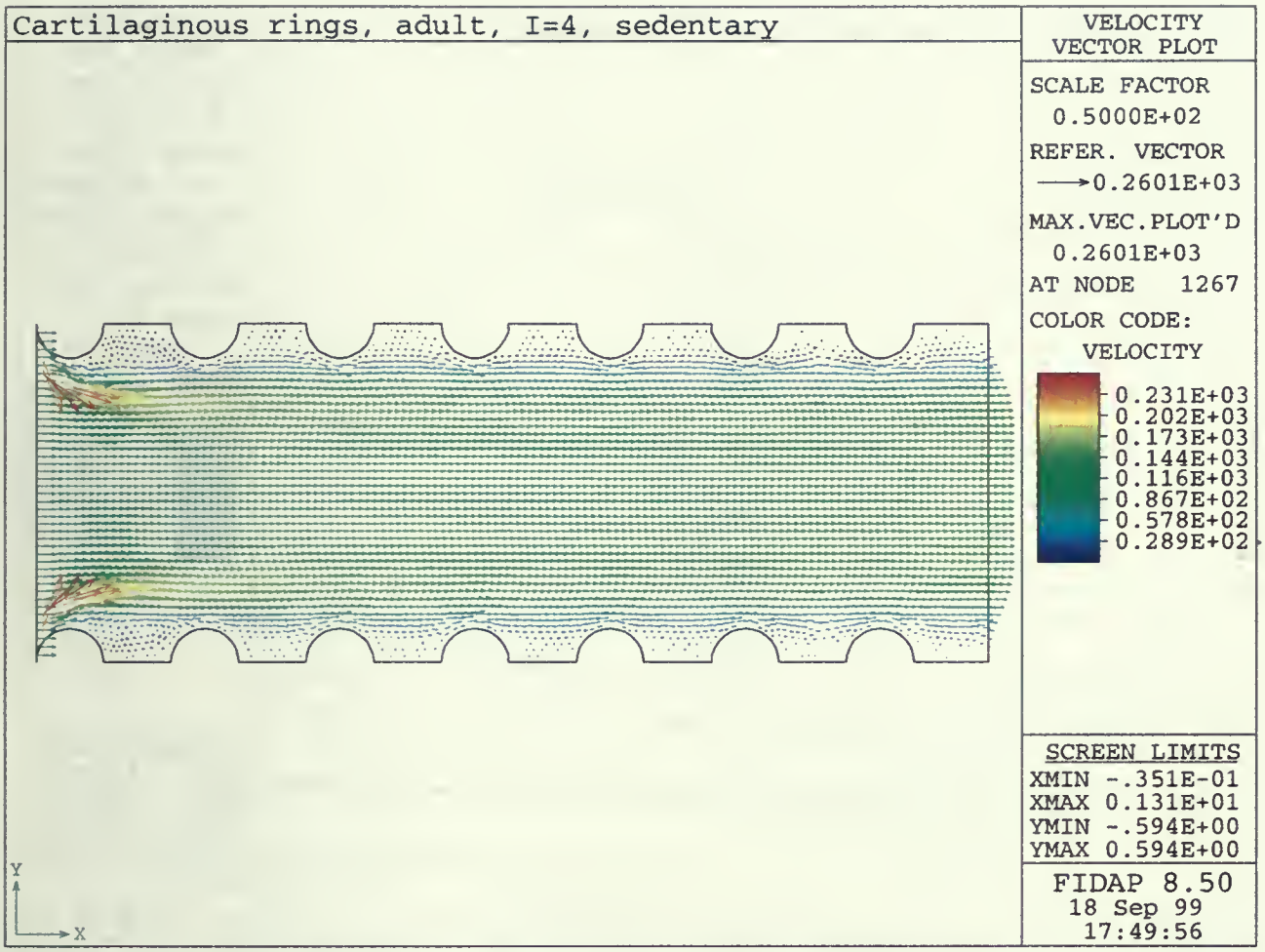

Fig. 19. Convective flow field in the bronchus of Figure 18 as calculated using a computational fluid dynamics code. Vector lengths and arrows indicate the magnitude and direction of flow.

have described deposition by one mechanism (eg, inertial impaction) with a parabolic velocity profile and deposition by another mechanism (eg, sedimentation) with a uniform velocity profile. Though this may have been a convenient path to follow (ie, using available deposition formulas from the literature without regard for their applicability), it was clearly an inconsistent approach. There are several problems with such an approach. Obviously there will be technical discrepancies when assumptions are invalid. However, the most serious problem is one of concept or the lack of mathematical rigor; that is, how can one assume that different velocity profiles (eg, parabolic and uniform) exist simultaneously at an identical location within the lung? The self-consistent set of formulas of Martonen[52] was derived to avoid this problem. For the sake of brevity, those deposition formulas are not printed here; the interested reader is referred to the original publication of Martonen[43] for details.

It should be noted that the particle dosimetry models most widely used throughout the world are those prepared to simulate the behavior of inhaled radionuclides for health effects analyses. They are the models of the National Council on Radiation Protection (see Chang et al[93] and Phalen et al[89]), and the International Commission for Radiological Protection.[94] Another model, offered by the Netherlands' National Institute of Public Health and the Environment, termed the RIVM model, has become popular in Europe.[95] Although the respective models are intended for risk assessment purposes, they are routinely used for other applications. However, the National Council on Radiation Protection, International Commission for Radiological Protection, and RIVM models are not physiologically

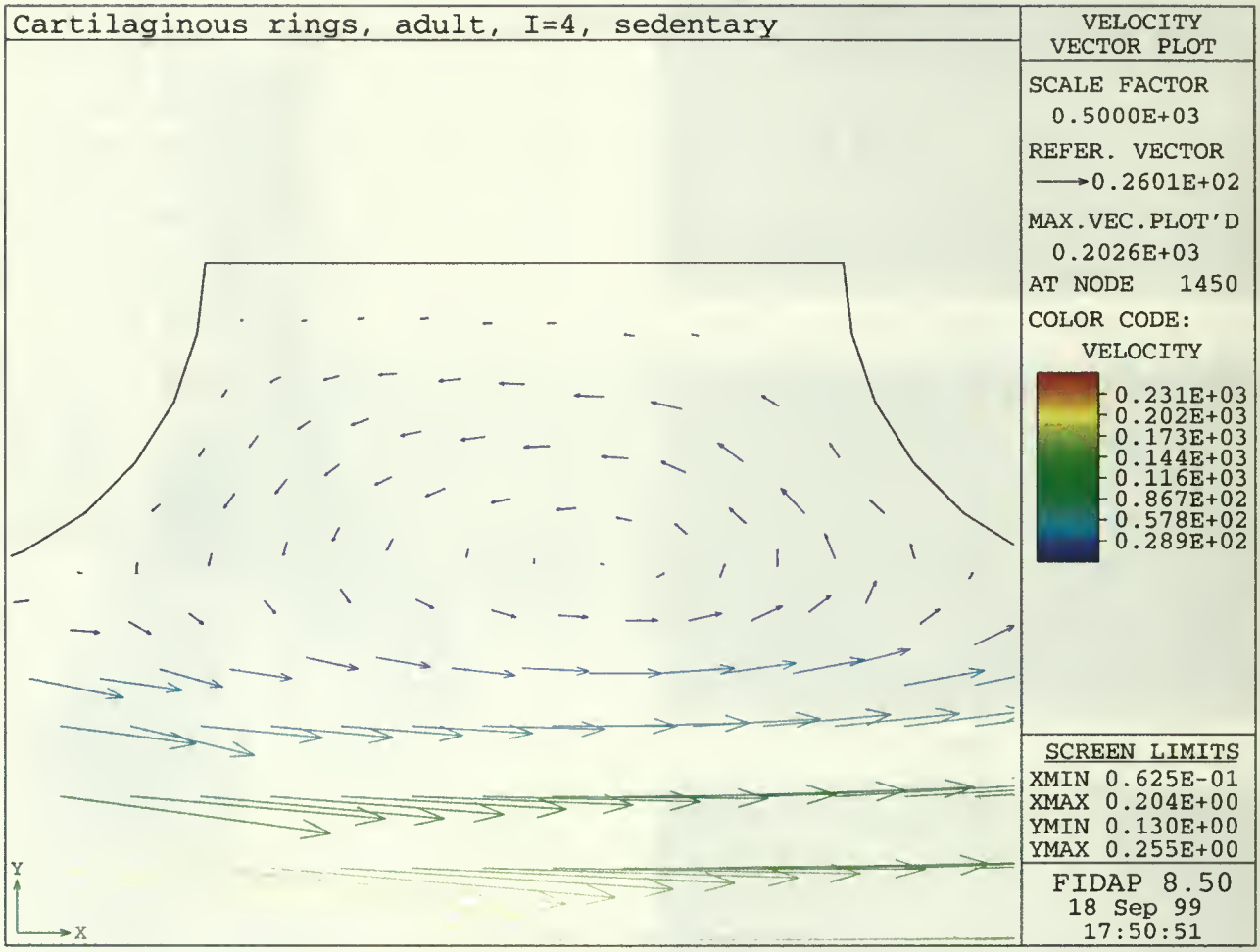

Fig. 20. Localized vortices caused by the presence of cartilaginous rings.

realistic. To be specific, they do not account for the real inner surface features of airways such as cartilaginous rings and carinal ridges that are clearly evident in Figures 12 and 13.

Results and Discussion

Airway Cast Experiments

To calculate particle deposition by diffusion in human airways, authors (eg, Yeh and Schum,[21] Yu and Diu,[87] Egan and Nixon,[88] Phalen et al,[89] and Anjilvel and Asgharian[90]) have chosen from the series of formulas presented by Ingham.[55–57] However, those formulas are applicable only to smooth-walled tubes. Therefore, as documented in Figure 12, the assumptions used to derive the Ingham[55–57] formulas are not compatible with the upper airways of the human lung. To develop a physiologically realistic model, Martonen et al considered the effects of the naturally occurring rings on lung dosimetry issues. Their influence on the motion of air[35] and on the trajectories of inhaled particles[37,38] were formulated. The analyses demonstrated that the deposition efficiencies of ultrafine particles ($D_g < 0.1$ μm) would be underestimated by 30–40% if the presence of rings was ignored. The results of the investigation established that the formulas of Ingham[55–57] notably underestimated particle deposition; the data indicated that rings could have a major role on the behavior of submicron particles, which are primarily deposited by diffusion. The potential significance of diffusion should be recognized in aerosol therapy because, as shown in Figure 1, there may be a great number of such small particles in the aerosols produced by MDIs, DPIs, and nebulizers. However, the *mass* of drug contained in these inhaled submicron particles is low and thus their contribution to clinical outcomes could be less than that for larger particles.

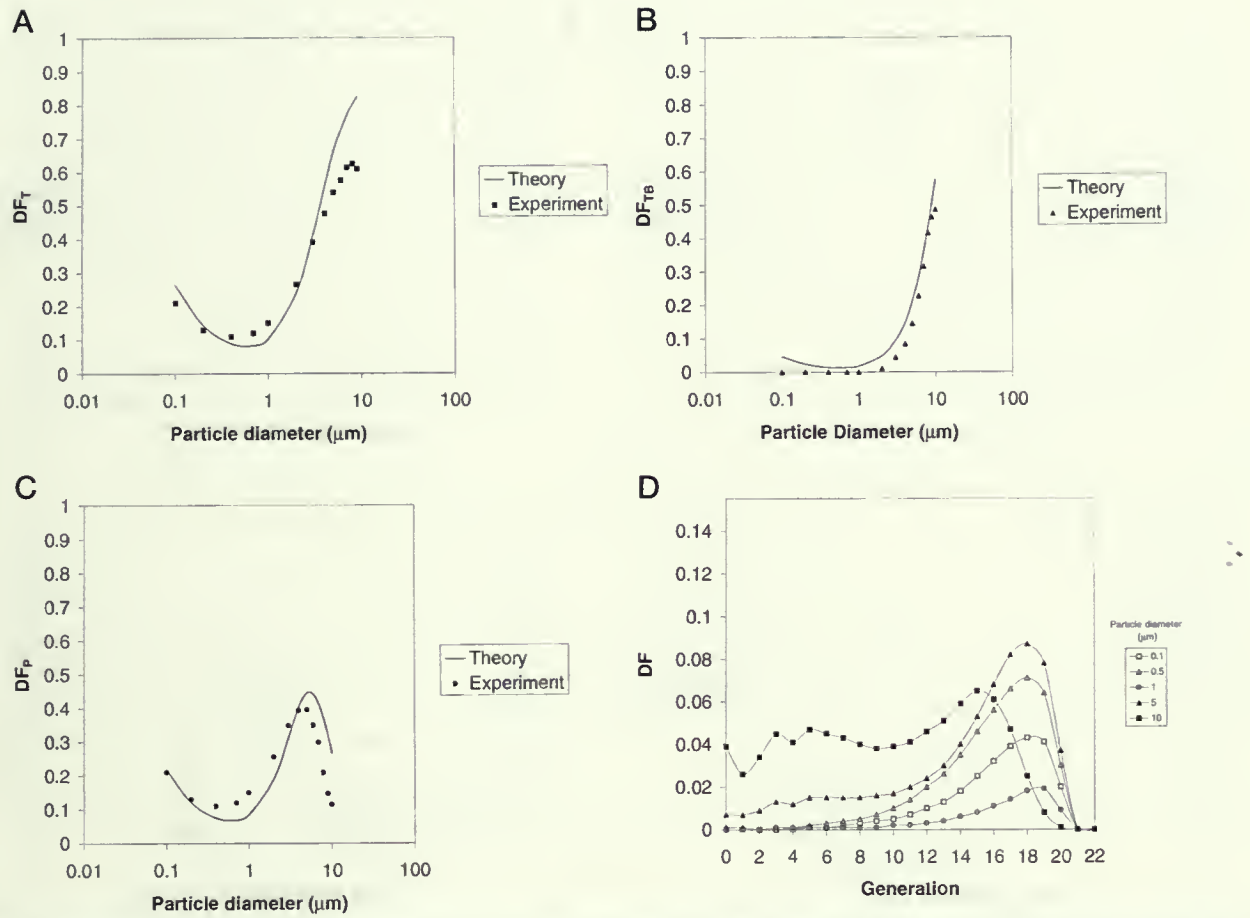

Fig. 21. Comparison of predicted and measured particle deposition patterns within human lungs. A: Total deposition fraction (DF_T). B: Tracheobronchial deposition fraction (DF_{TB}). C: Pulmonary deposition fraction (DF_P). The data reported by Heyder et al[98] are for geometric particle diameters (D_g) of unit density spheres under the following laboratory conditions: tidal volume = 500 mL, breathing frequency = 30 per minute. In Fig. 21D, the spatial distributions of the deposited aerosols are calculated on an airway generation-by-generation basis.

Cohen et al[96] and Cohen and Asgharian[97] performed particle deposition studies using replica casts of the human tracheobronchial tree. They measured particle deposition efficiencies and distributions within the casts. Subsequently, Zhang and Martonen[78,79] conducted computer simulations of the experiments. To resolve the question of which equations were most appropriate for human airways, they compared the Ingham[55–57] and the Martonen et al[37–38] formulas. The best agreement between modeling predictions and the Cohen et al[96] and Cohen and Asgharian[97] laboratory data were observed when the Martonen et al[37–38] formula was employed; that is, when the large bronchi were described as rough-walled tubes.

Human Subject Exposures

We shall now compare theoretically predicted values of particle deposition with experimental data. The human subject exposure studies performed by Heyder et al[98] will be simulated. In a systematic series of laboratory tests, they measured the deposition efficiencies of inhaled particles over a certain geometric size range related to unit density spheres and for well-defined breathing conditions.

Figures 21, 22, and 23 present the following deposition values: panel A: total lung deposition fraction; panel B: tracheobronchial deposition fraction; panel C: pulmonary (P) deposition fraction; and panel D: airway-by-airway deposition fraction within the lung.

In Figure 21, V_T is 500 mL and inspiration time (T_{in}) is 2 seconds. In Figure 22, V_T is 1,000 mL and T_{in} is 4 seconds. The inspiratory flow is the same in Figures 21 and 22 (ie, 250 mL/s), but the volume inhaled and commensurate depth of penetration into the lung is greater for Figure 22.

In Figure 23, V_T is 1,500 mL and T_{in} is 2 seconds. Therefore, although the inspiration *time* is the same as in Figure 21, the inspiratory *flow* is 750 mL/s. The effect of this higher flow is seen particularly on particles 5 μm and 10 μm in

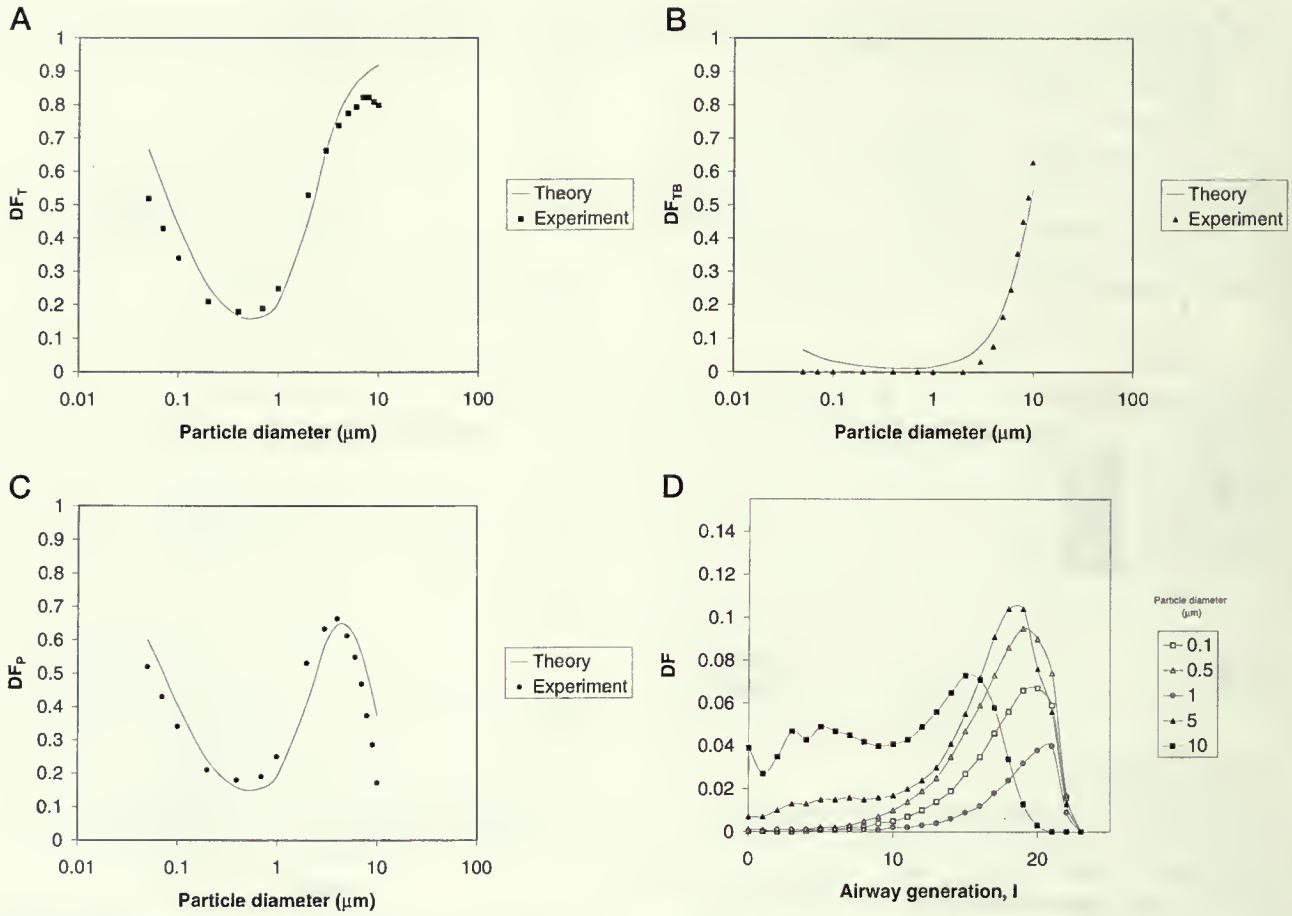

Fig. 22. Comparison of predicted and measured particle deposition patterns within human lungs. A: Total deposition fraction (DF_T). B: Tracheobronchial deposition fraction (DF_{TB}). C: Pulmonary deposition fraction (DF_P). The data reported by Heyder et al[98] are for geometric particle diameters (D_g) of unit density spheres under the following laboratory conditions: tidal volume = 1,000 mL, breathing frequency = 15 per minute. In Fig. 22D, the spatial distributions of the deposited aerosols are calculated on an airway generation-by-generation basis.

diameter, where there is increased deposition in more proximal airways (generations 0–6, Figures 21D and 23D).

The predicted deposition values in Figures 21–23 are in very good agreement with laboratory data over a wide particle size range, covering two orders of magnitude (0.1–10 μm). This is important to emphasize because, as was demonstrated in Figure 1, the polydisperse aerosols used in the medical arena include a sizeable fraction of submicron particles.

Thus, not only is total lung deposition (the A panels) accurately predicted, but its compartmental distribution (the B and C panels) is as well. This in turn influences particle clearance processes, which differ in both mode of action and efficiency of operation. In the tracheobronchial tree, deposited particles are removed by the mucociliary mechanism in 24–34 hours.[99] The time scale involved is quite different for the P region. Particles deposited in the alveolated airways may not be cleared for a matter of days, weeks, or months.[100] Clearance times obviously affect the corresponding residence times of drug within the respective lung compartments.

Based on the documented successful comparisons of the theoretically predicted particle deposition values with the data from human inhalation exposures, we believe that the lung dosimetry model has been validated. Therefore, in subsequent computations we shall apply the model to two problems of interest to the Aerosol Consensus Conference that are extremely difficult to address in the laboratory. They involve the subjects of heterogeneous dose distribution and pediatric medicine (ie, particle deposition in children).

Heterogeneous Dose Distribution Among Airways

Figures 21D, 22D, and 23D present the deposition patterns of inhaled particles within human lungs. The spa-

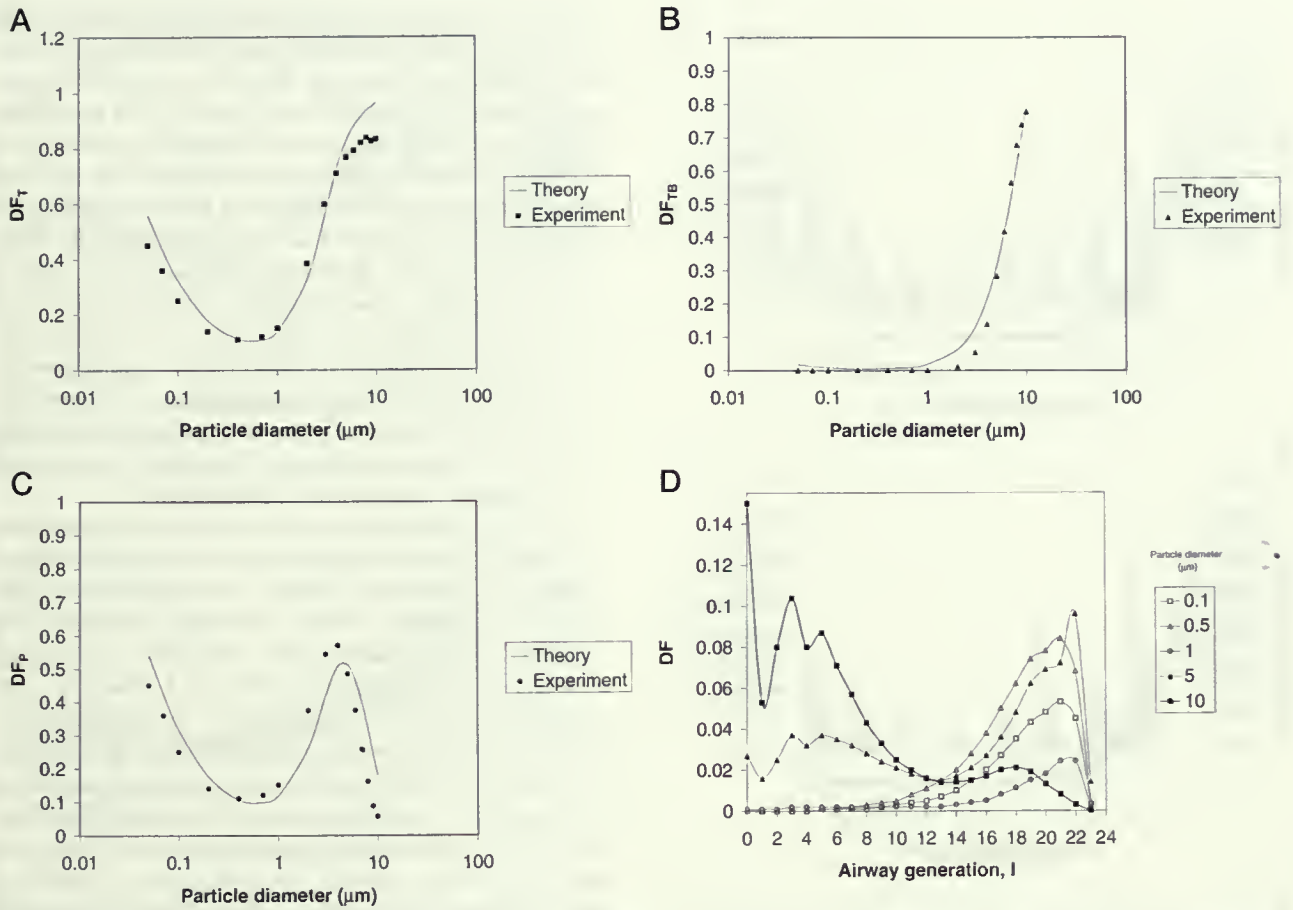

Fig. 23. Comparison of predicted and measured particle deposition patterns within human lungs. A: Total deposition fraction (DF_T). B: Tracheobronchial deposition fraction (DF_{TB}). C: Pulmonary deposition fraction (DF_P). The data reported by Heyder et al[98] are for geometric particle diameters (D_g) of unit density spheres under the following laboratory conditions: tidal volume = 1,500 mL, breathing frequency = 30 per minute. In Figure 23D, the spatial distributions of the deposited aerosols are calculated on an airway generation-by-generation basis.

tial distributions are very heterogeneous. The data are self-explanatory; we shall only comment that such deposition patterns are of seminal interest for aerosol therapy protocols involving both site-specific-acting drugs (eg, bronchodilators used in the treatment of asthma) and drugs intended for systemic delivery (eg, insulin).

The model has been employed to simulate a lung disease (cystic fibrosis). Specifically, it was used in the clinical environment to study the effects of disease-induced changes in patient ventilation and airway morphology on the deposition of inhaled particles.[101] The data indicate that airway diseases can exert a profound effect on the deposition of inhaled aerosol drugs. The advantage afforded by the model presented herein is that, since it has been validated, computer algorithms (ie, subroutines) can be written to describe disease states, and their effects predicted and accounted for in the administration of pharmacologic drugs.

Application to Pediatric Medicine

To describe drug dosimetry in children's lungs, it is necessary to define airway geometries for various ages, as well as corresponding elements of ventilation. We shall use the age-dependent morphologies presented by Hofmann et al,[102] Martonen et al,[39] and Martonen and Zhang.[103] The associated breathing conditions are given in Table 3.

In Figures 15A, 15B, and 15C the mean velocity values in human lungs as a function of subject age are presented for the sedentary, and light and heavy breathing. There is a quasi-monotonic relationship among the plots; namely, velocities are most often greatest in the youngest child (ie, the 7-month-old) and usually decrease with age, being least in the adult. An interesting feature is that the family of plots in Panels 15A, 15B, and 15C seem to converge

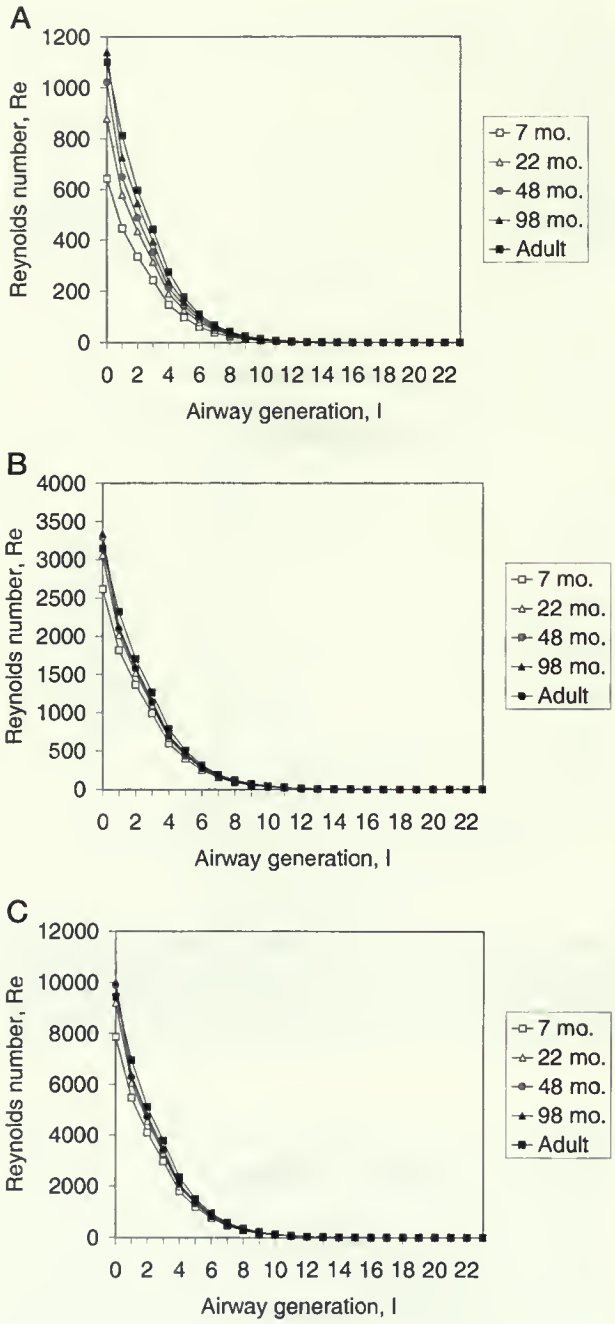

Fig. 24. Reynolds numbers for fluid motion within human lungs as a function of subject age. A: Sedentary. B: Light activity. C: Heavy activity. Related information is given in Figure 15.

and approach zero at the same location, the entrance to the acinar regions of the respective lungs.

Figure 24A, 24B, and 24C present the Reynolds numbers for the aforementioned velocity values. As previously defined, $Re = dv\mu/\rho$, where v, μ, and ρ are the mean velocity, absolute viscosity, and density of the fluid. This information is provided because the Re values are typically used in the literature to identify fluid dynamics conditions. It will permit the interested reader to relate our computations to other published works. We must emphasize, however, that it is very difficult to unambiguously relate Re values *per se* with local flow conditions in lung airways with respect to whether or not flow in them is laminar or turbulent. In standard engineering parlance, the transition from laminar to turbulent motion is accepted to occur at a given Re magnitude; for example, Schlichting[104] suggests a value of $Re \approx 2300$. But, that condition applies to idealized tubes that are straight, smooth-walled, sufficiently long, rigid, and of circular cross-section. Few, if any, airways of the lung possess those physical features. Therefore, caution must be advised when extrapolating calculated Re values to in vivo situations. This subject was treated in a systematic study of air flow patterns.[34–36,105]

In Figure 25 particle deposition patterns are presented as a function of human subject age for sedentary breathing conditions, as defined in Table 3. The deposition data are given in a systematic manner to facilitate use: Panel A is the total deposition fraction, DF_T; Panel B is the tracheobronchial deposition fraction, DF_{TB}; and, Panel C is the pulmonary deposition fraction, DF_P. To be consistent with the manner in which experimental data from the literature have been published, the respective values are normalized to the quantity of aerosol entering the trachea. The findings are self-explanatory, but a few observations may be in order to orient the reader. The data create a family of curves that seem to be rather similar. That is, the curves have the same shapes for lung (DF_T) and compartmental (DF_{TB} and DF_P) deposition and do not differ too much in magnitude.

In Figures 26A, 26B, and 26C, the data from Figure 25 are normalized to the airway surface area. Thus, in Panel 26A, the total quantity of aerosol deposited in the lung is divided by the total surface area of the lung. In Panel 26B the quantity of aerosol deposited in the tracheobronchial compartment is divided by the surface area of those airways. In Panel 26C the quantity of aerosol deposited in the P compartment is divided by its surface area.

For demonstration purposes, let us consider the inhalation of a 3 μm particle. As seen in Panel 26A, the lungs of a 7-month-old child, when compared to an adult, have about a factor of 8 more aerosol deposition. The corresponding compartmental distribution can be discerned by examining Panels 26B and 26C. It is clear that children receive approximately 4-fold greater dosages of inhaled drugs than adults, when airway surface area is factored into the dose calculations.

Summary

The most widely used particle dosimetry models are those proposed by the National Council on Radiation

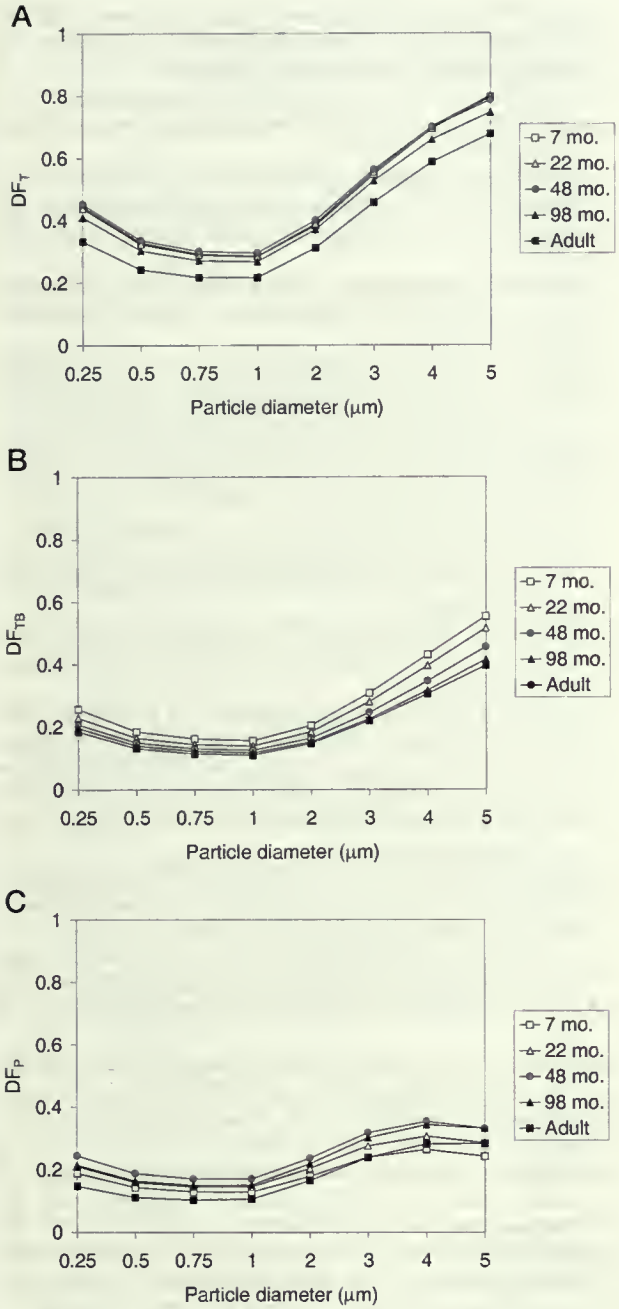

Fig. 25. Predicted particle deposition patterns in human lungs as a function of subject age. A: Total. B: Tracheobronchial. C: Pulmonary. See text for definitions of terms.

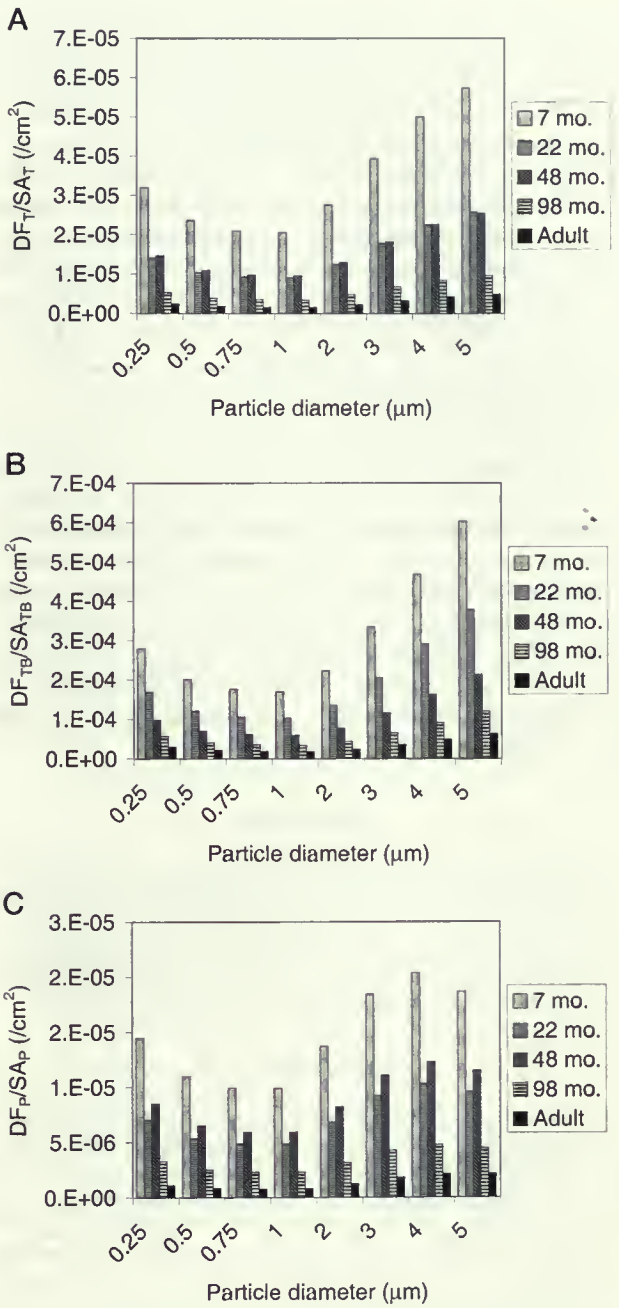

Fig. 26. Predicted particle deposition patterns in human lungs as a function of subject age, normalized to the respective airway surface areas. A: Total. B: Tracheobronchial. C: Pulmonary. See text for definitions of terms. DF_{TB} = tracheobronchial deposition fraction. SA_{TB} = tracheobronchial surface area.

Protection, International Commission for Radiological Protection, and the Netherlands National Institute of Public Health and the Environment (the RIVM model). Those models have inherent problems that may be regarded as serious drawbacks; for example, they are not physiologically realistic. They ignore the presence and commensurate effects of naturally occurring structural elements of lungs (eg, cartilaginous rings, carinal ridges), which have been demonstrated to affect the motion of inhaled air. Most importantly, the surface structures have been shown to influence the trajectories of inhaled particles transported by air streams. Thus, the model presented herein by Martonen et al may be perhaps the most appropriate for human lung dosimetry.

In its present form, the model's major "strengths" are that it could be used for diverse purposes in medical research and practice, including: to target the delivery of drugs for diseases of the respiratory tract (eg, cystic fibrosis, asthma, bronchogenic carcinoma); to selectively deposit drugs for systemic distribution (eg, insulin); to design clinical studies; to interpret scintigraphy data from human subject exposures; to determine laboratory conditions for animal testing (ie, extrapolation modeling); and to aid in aerosolized drug delivery to children (pediatric medicine). Based on our research, we have found very good agreement between the predictions of our model and the experimental data of Heyder et al,[98] and therefore advocate its use in the clinical arena.

In closing, we would note that for the simulations reported herein the data entered into our computer program were the actual conditions of the Heyder et al[98] experiments. However, the deposition model is more versatile and can simulate many aerosol therapy scenarios. For example, the core model has many computer subroutines that can be enlisted to simulate the effects of aerosol polydispersity,[44] aerosol hygroscopicity,[103] patient ventilation,[42] patient lung morphology,[45] patient age,[39] and patient airway disease.[101]

DISCLAIMER

This manuscript has been reviewed in accordance with the policy of the National Health and Environmental Effects Research Laboratory, United States Environmental Protection Agency, and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

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REFERENCES

1. Barnes PJ, Basbaum CB, Nadel JA, Roberts JM. Localization of b-adrenoreceptors in mammalian lung by light microscopic autoradiography. Nature 1982;299(5882):444–447.
2. Hensley MJ, O'Cain CF, McFadden ER Jr, Ingram RH. Distribution of bronchodilation in normal subjects beta agonist versus atropine. J Appl Physiol 1978;45(5):778–782.
3. Newhouse MT, Ruffin RE. Deposition and fate of inhaled aerosols. Chest 1978;73(6 Suppl):936–943.
4. Ruffin RE, Dolovich MB, Wolff RK, Newhouse MT. The effects of preferential deposition of histamine in the human airway. Am Rev Respir Dis 1978;117(3): 485–492.
5. Ruffin RE, Dolovich MB, Oldenberg FA Jr, Newhouse MT. The preferential deposition of inhaled isoproterenol and propranolol in asthmatic patients. Chest 1981;80(Suppl):904–907.
6. Clay MM, Pavia D, Clarke SW. Effect of aerosol particle size on bronchodilatation with nebulised terbutaline in asthmatic subjects. Thorax 1986;41(5):364–368.
7. Mitchell DM, Solomon MA, Tolfree SEJ, Short M, Spiro SG. Effect of particle size of bronchodilator aerosols on lung distribution and pulmonary function in patients with chronic asthma. Thorax 1987; 42(6):457–461.
8. Karlsson JA, Sant'Ambrogio G, Widdicombe J. Afferent neural pathways in cough and reflex bronchoconstriction (review). J Appl Physiol 1988;65(3):1007–1023.
9. Persson G, Wiren JE. The bronchodilator response from inhaled terbutaline is influenced by the mass of small particles: a study on a dry powder inhaler (Turbuhaler). Eur Respir J 1989;2(3):253–256.
10. Smaldone GC, Walser L, Perry RJ, Ilowite JS, Bennett WD, Greco M. Generation and administration of aerosols for medical and physiological research studies. J Aerosol Med 1989;2:81–87.
11. Anderson PJ, Garshick E, Blanchard JD, Feldman HA, Brain JD. Intersubject variability in particle deposition does not explain variability in responsiveness to methacholine. Am Rev Respir Dis 1991; 144(3 Pt 1):649–654.
12. Ashworth HL, Wilson CG, Sims EE, Wotton PK, Hardy JG. Delivery of propellant soluble drug from a metered dose inhaler. Thorax 1991;46(4):245–247.
13. Martonen TB. Aerosol therapy implications of particle deposition patterns in simulated human airways. J Aerosol Med 1991;4:25–40.
14. Mortensen J, Groth S, Lange P, Hermansen F. Effect of terbutaline on mucociliary clearance in asthmatic and healthy subjects after inhalation from a pressurised inhaler and a dry powder inhaler. Thorax 1991;46(11):817–823.
15. Newman SP, Weisz AWB, Taalee N, Clarke SW. Improvement of drug delivery with a breath actuated pressurized aerosol for patients with poor inhaler technique. Thorax 1991;46(10):712–716.
16. Vidgren M, Silvasti M, Vidgren P, Laurikainen K, Lehti H, Paronen P. Physical properties and clinical efficacy of two sodium cromoglycate inhalation aerosol preparations. Acta Pharm Nord 1991;3(1): 1–4.
17. Vidgren P, Vidgren M, Laurikainen K, Pietila T, Silvasti M, Paronen P. In vitro deposition and clinical efficacy of two sodium cromoglycate inhalation powders. Int J Clin Pharmacol Ther Toxicol 1991; 29(3):108–112.
18. Groth ML, Foster WM. Aerosolized atropine sulfate influence of inhalation pattern on effective blockade of vagal airway tone. Am Rev Respir Dis 1992;145(1):215–219.
19. Hofmann W, Koblinger L. Monte Carlo modeling of aerosol deposition in human lungs. Part II: Deposition fractions and their sensitivity to parameter variation. J Aerosol Sci 1990;21:675–688.
20. Bergmann R, Hofmann W, Koblinger L. Particle deposition modeling in the human lung: comparison between Monte Carlo and ICRP model predictions. J Aerosol Sci 1997;28(Suppl 1): S433–S434.
21. Yeh HC, Schum GM. Models of human lung airways and their application to inhaled particle deposition. Bull Math Biol 1980;42(3): 461–480.
22. Martonen TB, Yang Y. Deposition mechanics of pharmaceutical particles in human airways. In: Hickey AJ editor. Inhalation aerosols: physical and biological basis for therapy. New York: Marcel Dekker; 1996: 3–27.
23. Horsfield K, Cumming G. Angles of branching and diameters of branches in the human bronchial tree. Bull Math Biophys 1967; 29(2):245–259.
24. Horsfield K, Dart G, Olson DE, Filley GF, Cumming G. Models of the human bronchial tree. J Appl Physiol 1971;31(2):207–217.

25. Horsfield K. Pulmonary airways and blood vessels considered as confluent trees. In: Crystal RG, West JB, Barnes PJ, Cherniack NS, Weibel ER, editors. The lung: scientific foundations. Vol 1. New York: Raven Press; 1991: 721–727.
26. Weibel ER. Morphometry of the human lung. New York: Academic Press; 1963.
27. Weibel ER. Design of airways and blood vessels as branching trees. In: Crystal RG, West JB, Barnes PJ, Cherniack NS, Weibel ER, editors. The lung: scientific foundations. Vol 1. New York: Raven Press; 1991: 711–720.
28. Martonen TB, Yang Y, Dolovich M. Definition of airway composition within gamma camera images. J Thorac Imaging 1994;9(3): 188–197.
29. Martonen TB, Yang Y, Dolovich M, Guan X. Computer simulations of lung morphologies within planar gamma camera images. Nucl Med Commun 1997;18(9):861–869.
30. Martonen TB, Yang Y, Hwang D, Fleming JS. Mapping the human lung using Delaunay tessellation. Comp Biomed Res 1994;27(4): 245–262.
31. Martonen TB, Yang Y, Hwang D, Fleming JS. Computer model of human lung morphology to complement SPECT analyses. Int J Biomed Comput 1995;40(1):5–16.
32. Martonen TB, Yang Y, Hwang D, Fleming JS. Computer simulations of human lung structures for medical applications. Comput Biol Med 1995;25(5):431–446.
33. Martonen TB, Hwang D, Guan X, Fleming JS. Supercomputer description of human lung morphology for imaging analysis. J Nucl Med 1998;39(4):745–750.
34. Martonen TB, Zhang Z, Lessmann R. Fluid dynamics of the human larynx and upper tracheobronchial airways. Aerosol Sci Tech 1993; 19:133–156.
35. Martonen TB Yang Y, Xue Z. Influences of cartilaginous rings on tracheobronchial fluid dynamics. Inhal Toxicol 1994;6:185–203.
36. Martonen TB, Yang Y, Xue Z. Effects of carinal ridge shapes on lung air streams. Aerosol Sci Tech 1994;21:119–136.
37. Martonen TB, Zhang Z, Yang Y, Bottei G. Airway surface irregularities promote particle diffusion in the human lung. Radiat Prot Dosim 1995;59:5–14.
38. Martonen TB, Zhang Z, Yang Y. Particle diffusion from developing flows in rough-walled tubes. Aerosol Sci Tech 1997;26:1–11.
39. Martonen TB, Graham RC, Hofmann W. Human subject age and activity level: factors addressed in a biomathematical deposition program for extrapolation modeling. Health Phys 1989;57(Suppl 1):49–59.
40. Heyder J, Gebhart J, Stahlhofen W, Stuck B. Biological variability of particle deposition in the human respiratory tract during controlled and spontaneous mouth-breathing. Ann Occup Hyg 1982;26(1–4): 137–147.
41. Kim CS, Hu SC. Regional deposition of inhaled particles in human lungs: comparison between men and women. J Appl Physiol 1998; 84(6):1834–1844.
42. Martonen TB, Katz IM. Deposition patterns of aerosolized drugs within human lungs: effects of ventilatory parameters. Pharm Res 1993;10(6):871–878.
43. Martonen TB. Mathematical model for the selective deposition of inhaled pharmaceuticals. J Pharm Sci 1993;82(12):1191–1199.
44. Martonen TB, Katz I. Deposition patterns of polydisperse aerosols within human lungs. J Aerosol Med 1993;6:251–274.
45. Martonen TB, Katz I. Inter-related effects of morphology and ventilation on drug deposition patterns. STP Pharm Sci 1994;4:11–18.
46. Martonen TB, Zhang Z, Yang Y. Particle diffusion with entrance effects in a smooth-walled cylinder. J Aerosol Sci 1996;27(1):139–150.
47. Landahl HD, Herrmann RG. On the retention of airborne particulates in the human lung. J Ind Hyg Toxicol 1948;30:181–188.
48. Beeckmans JM. The deposition of aerosols in the respiratory tract. I. Mathematical analysis and comparison with experimental data. Can J Physiol Pharmac 1965;43:157–172.
49. Cheng YS, Wang CS. Inertial deposition of particles in a bend. J Aerosol Sci 1975;6:139–145.
50. Yeh HC. Comments on the paper: Inertial deposition of particles in a bend by YS Cheng and CS Wang. J Aerosol Sci 1976;7:275–276.
51. Crane RI, Evans RL. Inertial deposition of particles in a bent pipe. J Aerosol Sci 1977;8:161–170.
52. Martonen TB. Analytical model of hygroscopic particle behavior in human airways. Bull Math Biol 1982;44(3):425–442.
53. Landahl HD. On the removal of airborne droplets by the human respiratory tract. I. The lung. Bull Math Biophys 1950;12:43–56.
54. Wang CS. Gravitational deposition of particles from laminar flows in inclined channels. J Aerosol Sci 1975;6:191–204.
55. Ingham DB. Diffusion of aerosols from a stream flowing through a cylindrical tube. J Aerosol Sci 1975;6:125–132.
56. Ingham DB. Diffusion of aerosols from a stream flowing through a short cylindrical tube. J Aerosol Sci 1984;15:637–641.
57. Ingham DB. Diffusion of aerosols in the entrance region of a smooth cylindrical pipe. J Aerosol Sci 1991;22:253–257.
58. Foord N, Black A, Walsh M. Regional deposition of 2.5–7.5 μm diameter inhaled particles in healthy male non-smokers. J Aerosol Sci 1978;9:343–357.
59. Chan TL, Lippmann M. Experimental measurements and empirical modelling of the regional deposition of inhaled particles in humans. Am Ind Hyg Assoc J 1980;41(6):399–409.
60. Stahlhofen W, Gebhart J, Heyder J. Experimental determination of the regional deposition of aerosol particles in the human respiratory tract. Am Ind Hyg Assoc J 1980;41(6):385–398.
61. Hiller FC, Mazumder MK, Wilson JD, McLeod PC, Bone RC. Human respiratory tract deposition using multimodal aerosols. J Aerosol Sci 1982;13(4): 337–343.
62. Schlesinger RB, Gurman JL, Lippmann M. Particle deposition within bronchial airways: comparisons using constant and cyclic inspiratory flows. Ann Occup Hyg 1982;26(1–4):47–64.
63. Bennett WD, Messina MS, Smaldone GC. Effect of exercise on deposition and subsequent retention of inhaled particles. J Appl Physiol 1985;59(4):1046–1054.
64. Wilson LB. The deposition of charged particles in tubes with reference to the retention of therapeutic aerosols in the human lung. J Colloid Sci 1947;2:271–276.
65. Chan TL, Yu CP. Charge effects on particle deposition in the human tracheobronchial tree. Ann Occup Hyg 1982;26(1–4):65–75.
66. Tarroni G, Melandri C, Prodi V, De Zaiacomo T, Formignani M, Bassi P. An indication on the biological variability of aerosol total deposition in humans. Am Ind Hyg Assoc J 1980;41(11):826–831.
67. Melandri C, Tarroni G, Prodi V, De Zaiacomo TG, Formignani M, Lombardi CC. Deposition of charged particles in the human airways. J Aerosol Sci 1983;14:657–669.
68. Chan TL, Lippman M, Cohen VR, Schlesinger RB. Effect of electrostatic charges on particle deposition in a hollow cast of the human larynx-tracheobronchial tree. J Aerosol Sci 1978;9:463–468.
69. Cohen BS, Xiong JQ, Fang CP, Li W. Deposition of charged particles on lung airways. Health Phys 1998;74(5):554–560.
70. Gonda I, Khalik AFA. On the calculation of aerodynamic diameters of fibres. Aerosol Sci Technol 1985;4:233–238.
71. Chan HK, Gonda I. Respirable form of crystals of cromoglycic acid. J Pharm Sci 1989;78(2):176–180.
72. Johnson DL, Martonen TB. Behavior of inhaled fibers: potential applications to medicinal aerosols. Part Sci Technol 1994;12:161–173.

73. Johnson DL, Polikandritou-Lambros M, Martonen TB. Drug encapsulation and aerodynamic behavior of a lipid microtubule aerosol. Drug Delivery 1996;3:9–15.
74. Fuchs NA. The mechanics of aerosols. London: Pergamon Press; 1964.
75. Martonen TB, Hofmann W, Lowe JE. Cigarette smoke and lung cancer (review). Health Phys 1987;52(2):213–217.
76. Martonen TB. Deposition patterns of cigarette smoke in human airways. Am Ind Hyg Assoc J 1992;53:6–18.
77. Langhaar HL. Steady flow in the transition length of a straight tube. J Appl Mech 1942;9:55–58.
78. Zhang Z, Martonen TB. Comparison of theoretical and experimental particle diffusion data within human airway casts. Cell Biochem Biophys 1996;27(2):97–108.
79. Zhang Z, Martonen TB. Deposition of ultrafine aerosols in human tracheobronchial airways. Inhal Toxicol 1997;9:99–110.
80. Schroter RC, Sudlow MF. Flow patterns in models of the human bronchial airways. Respir Physiol 1969;7(3):341–355.
81. Olson DE, Dart GA, Filley GF. Pressure drop and fluid flow regime of air inspired into the human lung. J Appl Physiol 1970;28(4):482–494.
82. Sudlow MF, Olson DE, Schroter RC. Fluid mechanics of bronchial air-flow. In: Walton WH, editor. Inhaled particles III. Surrey England: Gresham Press; 1971: 19–31.
83. Olson DE, Sudlow MF, Horsfield K, Filley GF. Convective patterns of flow during inspiration. Arch Intern Med 1973;131(1):51–57.
84. Chang HK, El Masry OA. A model study of flow dynamics in human central airways. Part I: axial velocity profiles. Respir Physiol 1982; 49(1):75–95.
85. Isabey D, Chang HK. A model study of flow dynamics in human central airways. Part II: secondary flow velocities. Respir Physiol 1982;49(1):97–113.
86. Musante CJ, Martonen TB. Computational fluid dynamics in human lungs: I. Effects of natural airway features. Medical Applications of Computer Modelling and Fluid Dynamics: Respiratory System. Martonen TB, editor. Computational Mechanics Publications Ashurst (in press).
87. Yu CP, Diu CK. A comparative study of aerosol deposition in different lung models. Am Ind Hyg Assoc J 1982;43(1):54–65.
88. Egan MJ, Nixon W. A model of aerosol deposition in the lung for use in inhalation dose assessments. Radiat Prot Dosim 1985;11:5–17.
89. Phalen RF, Cuddihy RG, Fisher GL, Moss OR, Schlesinger RB, Swift DL, Yeh HC. Main features of the proposed NCRP respiratory tract model. Radiat Prot Dosim 1991;38:179–184.
90. Anjilvel S, Asgharian B. A multiple-path model of particle deposition in the rat lung. Fundam Appl Toxicol 1995;28(1):41–50.
91. Findeisen W. Uber das absetzen kleiner in der luft suspendierter teilchen in der menschlichen lunge bei der atmung. Pfluegers Arch Ges Physiol 1935;236:367–379.
92. Gormley PG, Kennedy M. Diffusion from a stream flowing through a cylindrical tube. Proc R Ir Acad 1949;52:163–169.
93. Chang IY, Griffith WC, Shyr LJ, Yeh HC, Cuddihy RG, Seiler FA. Software for the draft NCRP respiratory tract dosimetry model. Radiat Prot Dosim 1991;38:193–199.
94. ICRP. Human respiratory tract model for radiological protection. ICRP Publication 66 (United Kingdom: Elsevier) 1994.
95. Freijer JI, Cassee FR, van Bree L. Modeling of particulate matter deposition in the human airways. RIVM Report No. 624029 001 (National Institute of Public Health and the Environment Bilthoven the Netherlands) 1997.
96. Cohen BS, Sussman RG, Lippmann M. Ultrafine particle deposition in a human tracheobronchial cast. Aerosol Sci Technol 1990;12: 1082–1091.
97. Cohen BS, Asgharian B. Deposition of ultrafine particles in the upper airways: an empirical analysis. J Aerosol Sci 1990;21:789–795.
98. Heyder J, Gebhart J, Rudolf G, Schiller CF, Stahlhofen W. Deposition of particles in the human respiratory tract in the size range 0.005–15 μm. J Aerosol Sci 1986;17(5):811–825.
99. Smaldone GC, Perry RJ, Bennett WD, Messina MS, Zwang J, Ilowite J Interpretation of "24 hour lung retention" in studies of mucociliary clearance. J Aerosol Med 1988;1:11–20.
100. Foster WM. Is 24-hour lung retention an index of alveolar deposition? J Aerosol Med 1988;1:1–10.
101. Martonen TB, Katz I, Cress W. Aerosol deposition as a function of airway disease: cystic fibrosis. Pharm Res 1995;12(1):96–102.
102. Hofmann W, Martonen TB, Graham RC. Predicted deposition of nonhygroscopic aerosols in the human lung as a function of subject age. J Aerosol Med 1989;2:49–68.
103. Martonen TB, Zhang Z. Deposition of sulfate acid aerosols in the developing human lung. Inhal Toxicol 1993;5:165–187.
104. Schlichting H. Boundary layer theory. New York: McGraw Hill; 1968.
105. Martonen TB, Yang Y, Xue Z, Zhang Z. Motion of air within the human tracheobronchial tree. Partic Sci Tech 1994;12:175–188.

Assessment End Points for Inhaled Drug Delivery

Paula J Anderson MD

Introduction
Theoretical Models
In Vitro Measurements
Scintigraphic Measurements
Pharmacokinetics and Pharmacodynamics
Clinical Outcomes
- **Spirometry**
- **Peak Expiratory Flow**
- **Bronchoprovocation**
- **Markers of Inflammation**
- **Concomitant Care**
- **Symptoms**
- **Quality of Life**
- **Toxicity**

Summary

[Respir Care 2000;45(6):737–755] *Key words: aerosol, end point, pharmacokinetic, pharmacodynamic, outcome.*

Introduction

How do we assess aerosolized drug delivery? The options are numerous and range from computerized predictions to patients' opinions. The number of variables involved in delivering aerosolized drugs to the respiratory tract imparts an unusual degree of complexity, as well as importance, to the measurement of outcomes. Variances at any step in the delivery process can affect the ultimate result, including changes in drug formulation, delivery device, administration skill, and breathing pattern and lung anatomy due to disease. Figure 1 presents a schema for approaching the discussion of assessment end points. The various approaches represent a continuum from techniques that predict the dose of aerosolized drug, to those that measure the dose, to those that quantify the effect of the dose. Each level of assessment is important in the development of an inhaled drug or delivery device, with predictions and measurements of delivered dose constituting the groundwork for the essential assessment of efficacy in human subjects. To designate the best assessment end point requires value judgments about the desired outcome, and may vary with the drug and disease state. The perspective about the optimal outcome may also differ among scientists, clinicians, patients, regulatory agencies, and third-party payers.

Theoretical Models

Mathematical models were originally developed in the field of industrial hygiene and radiation protection for prediction of the behavior of inhaled mineral and occupational dusts.[1] Using models, estimates could be made about amount and location of particle deposition based on particle size characteristics and breathing patterns. Early models were simplistic, with basic lung morphologies and the assumption of stable particle size and behavior. Since then, models have become increasingly sophisticated, with more detailed lung morphology, and options for breathing pat-

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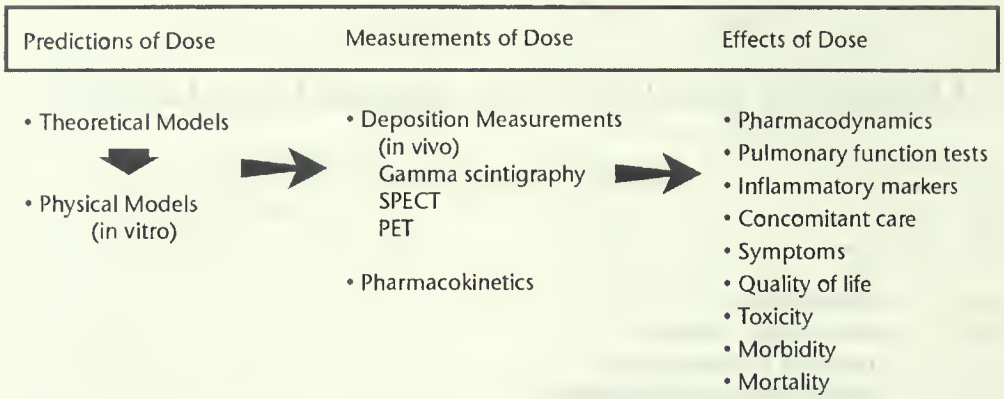


Fig. 1. Schematic of assessment end points in the evaluation of inhaled drug delivery.

terns, gender, and age.[2–5] Validation of these models with experimental data has been an essential step for confirmation of their predictions, but for the most part these experimental measurements have been conducted in normal adults with monodisperse, stable particles and highly regimented breathing patterns.[6,7] This situation does not closely resemble that of a patient with severe obstructive lung disease inhaling a dose of bronchodilator from a metered-dose inhaler (MDI). Therapeutic aerosols introduce much more complexity into theoretical modeling. The aerosols are polydisperse and concentrated, and particles may change in size because of evaporation or hygroscopic growth. The formulations may be solutions, suspensions, or powders, and the inhaled cloud may be affected by particle-particle interactions and velocity profiles. In an attempt to deal with the challenges presented by therapeutic aerosols, models have been developed that account for particle hygroscopicity and polydispersity.[8–10]

Though progress has been made in modeling therapeutic drug particles, modeling of the alterations in flow and geometry in the diseased lung presents a greater challenge. Even in normal lungs, there is considerable intersubject variability in particle deposition measurements. This variability is magnified in diseased lungs because of alterations in airway dimensions, secretions, dynamic flow profiles, and breathing patterns. Morphology and physiology also vary widely with the type of lung disease. Experimental studies have shown that airway obstruction changes the amount and location of particle deposition,[11–14] and these changes vary with the degree of obstruction. Conversely, restrictive lung disease may not alter the quantity of deposited particles.[15] Attempts have been made to model the flow alterations caused by airway obstruction,[16] but this remains a very challenging area. To date, no model adequately addresses the anatomic changes and flow dynamics introduced by lung diseases, particularly those with airway obstruction.

There is increasing interest in using theoretical models to target particle deposition to specific lung sites, depending on the application.[10,17] Particle size and breathing patterns can be optimized to increase deposition amounts in certain areas of the respiratory tract. For example, bronchodilators might be more effective if delivered to airways where receptors are located, whereas drugs intended for systemic absorption would be best targeted to the alveoli, where absorption into the blood is more rapid. Inappropriate targeting could actually increase toxicity, such as in the case of a β-2 adrenergic aerosol that is delivered primarily to the alveoli and results in tachycardia and tremor, or an inhaled steroid that deposits primarily in the oropharynx, which can result in thrush. Mathematical models can be helpful in making projections about optimal particle size and breathing variables for development of a therapeutic aerosol and improving safety and efficacy of therapy. Predictions are an essential first step in drug development, and available models have become much more sophisticated on the subjects of particle characteristics and breathing variables. As measurement techniques become more sophisticated, it is important to continue to validate models with deposition measurements in human subjects. Intersubject variability in lung morphology and air flow are still major sources of variability in particle behavior that are difficult to predict with mathematical models.

In Vitro Measurements

The dose of aerosol deposited in the respiratory tract is greatly affected by the drug formulation, delivery device, and the device-patient interface. For this reason, in vitro models have been devised to measure the size characteristics and mass output of aerosol delivery devices. These types of measurements have been used to compare different types of devices[18,19] and to study variability among devices of the same type,[20] the effects of ambient conditions,[21] and combinations of drugs.[22] Determination of particle size distribution is a basic measurement that is usually performed with inertial impaction devices or optical

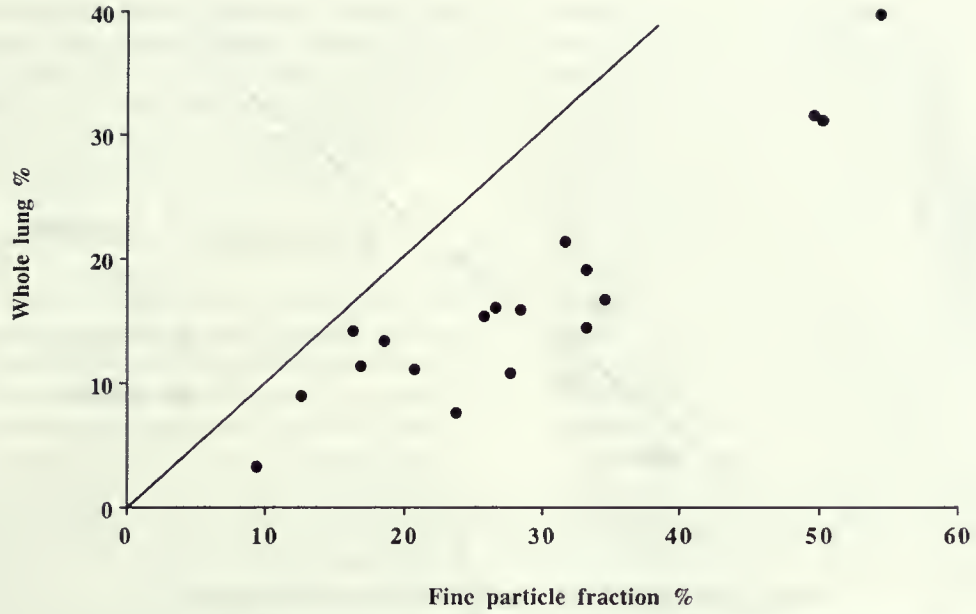


Fig. 2. Correlation of fine particle fraction measurement with scintigraphically measured lung deposition values from 11 studies of normal subjects using metered-dose inhalers and dry powder inhalers. Fine particle fraction was measured from stages 3 and 4 of a multistage liquid impinger. Correlation coefficient is 0.85 ($p < 0.01$), but fine particle fraction consistently overestimates lung deposition as measured by gamma scintigraphy. (From Reference 31, with permission.)

devices.[23–25] A cascade impactor draws the aerosol through a series of stages, each containing a plate or filter upon which the particles deposit according to their size. Optical methods use light scattering, diffraction, phase doppler, and time of flight measurements to derive particle size distribution. From these measurements, a mean aerodynamic diameter and the variability around that mean (geometric standard deviation) can be determined. These measurements are important for quality control and comparison of devices, and can be used to estimate the amount of deposition in the respiratory tract. It is inappropriate, however, to extrapolate these estimates to predictions of clinical efficacy.

Each measurement method has its drawbacks. For therapeutic aerosols, the amount of drug per particle may vary, depending on the formulation. The light scattering techniques measure particles whether or not they contain drug, whereas impaction devices have the advantage of using an assay of the amount of drug on each stage. Conversely, the high air flows used in impaction devices may cause aqueous particles to dry out, and these measurements may underestimate the actual particle sizes that would occur in the humid respiratory tract. Cascade impactor measurement with drug-specific assay is the method of choice in the United States, and a standard inlet manifold should be used. Quantification of the total emitted dose from nebulizers and inhalers should be performed using an absolute filter and specific drug assay. When gravimetric methods are used, evaporative losses may cause errors in estimating the amount of drug output. Recommendations are available for assessment of particle size distributions and mass output of nebulizers, MDIs, and dry powder inhalers (DPIs).[26–29]

Do in vitro measurements of particle size distribution and mass output accurately predict delivery of therapeutic aerosols to the patient? In an effort to address this question, aerosols have been delivered to cascade impactors or multistage impingers and "respirable fraction" or fine particle dose (usually percentage of particles $< 5–6$ μm diameter) compared to lung deposition measured in humans (Figs. 2 and 3).[30–32] In general, the in vitro predictions have overestimated lung deposition amounts, compared to those obtained in vivo by gamma scintigraphy or pharmacokinetic methods. The extent of agreement in these types of studies depends greatly on similarity of in vitro and in vivo protocols and on the definition of "respirable fraction" as measured by in vitro techniques. In vitro systems have also been modified in ways to more closely simulate the clinical scenario. Anatomic throats have been used with impactors or impingers instead of standard inlet manifolds.[32] Radiolabeled aerosols have been delivered to anatomic lung models using simulated breathing patterns so that total and regional deposition can be compared to human scintigraphic studies.[33,34] Other measurements of inhaled mass from a nebulizer have used a patient or patient surrogate (piston pump) breathing on a nebulizer through

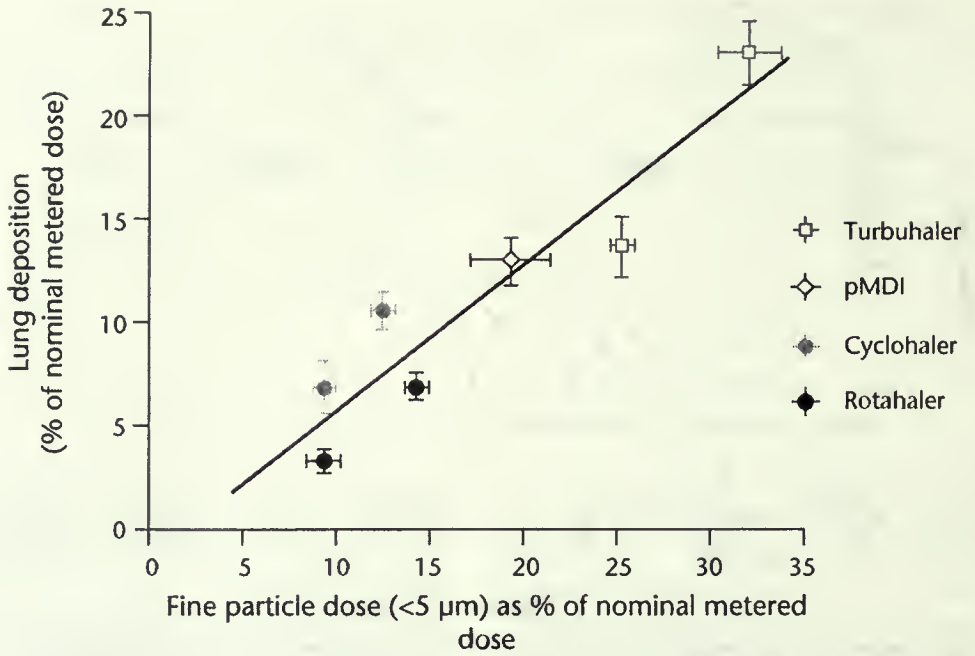


Fig. 3. Correlation of fine particle dose with lung deposition, as measured by charcoal block method in 11 healthy subjects inhaling albuterol from different dry powder inhalers (DPIs) and a metered-dose inhaler. DPI measurements were made at two flow rates. Fine particle dose was measured by cascade impactor with anatomic throat inlet. Fine particle dose is correlated with, but overestimates, lung deposition as measured by charcoal block (r = 0.94). (From Reference 32, with permission.)

filters.[35–37] When deposition of pentamidine was assessed in patients with human immunodeficiency virus by gamma scintigraphy versus filter measurements, there was good correlation between the two methods for lung deposition (Fig. 4).[35] The use of simulated breathing during in vitro testing does appear to greatly affect output measurements of medical nebulizers.[38,39] Models have also been developed to simulate delivery of aerosolized drugs to ventilated children[40] and adults.[41]

For all in vitro testing, it is essential that the model mimic as closely as possible the in vivo situation. The drug label, if one is used, should accurately reflect the behavior of the drug itself and not alter the inherent particle characteristics of the drug. Variables such as humidity, flow rate, and breathing pattern should be documented and controlled. It should be clear whether the goal of in vitro testing is quality control, comparison of drugs or devices, or to estimate delivery to the lungs. Though demonstrating adequate delivery during in vitro testing does not infer clinical efficacy, it is possible to show good correlation between in vitro measurements and in vivo lung deposition measurements. It is important to note, however, that the lung deposition measurements in many of these studies were made in healthy humans, not in subjects with lung disease. There continues to be a need for more studies comparing in vitro models with deposition measurements in patients with different lung diseases. Efforts should continue in the aerosol research community to standardize protocols for in vitro measurements of inhaled drugs. With development of expensive inhaled therapies such as anti-

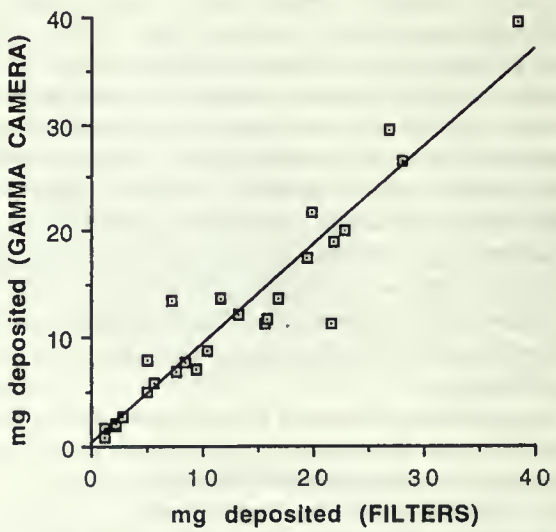


Fig. 4. Correlation of mass inhaled by filter method with lung deposition values measured by gamma scintigraphy in patients infected with human immunodeficiency virus (r = 0.95). Measurements were made using radiolabeled pentamidine administered via nebulizer. Inhaled and exhaled drug was collected on filters using patients' breathing patterns. (From Reference 35, with permission.)

biotics, recombinant products, and genetic therapy, much more attention is being given to proper design and testing of the delivery devices.[42,43] Prior to launching large, expensive clinical trials of therapeutic inhaled drugs, bench testing is essential to document the performance of the delivery device and optimize the trial design.

Scintigraphic Measurements

Total and regional deposition and clearance of therapeutic aerosols can be measured noninvasively by the use of inhaled radiolabeled particles and scintigraphic scanning techniques.[44,45] The distribution as well as quantity of label in the oropharynx, lungs, and gastrointestinal (GI) tract can be assessed, most often as two-dimensional images obtained via gamma camera. A more complicated and expensive methodology is single photon emission computed tomography, which provides three-dimensional tomographic views of the lungs.[46] Scintigraphic studies can also give information about mucociliary and cough clearance and epithelial permeability, but this section will focus on deposition measurements. Information about the site and extent of deposition of particles in the air spaces is invaluable and difficult to obtain by any other means. Understanding the behavior of therapeutic aerosols in vivo is a link between in vitro studies and clinical trials and helps to understand the efficacy (or lack thereof) and toxicity of inhaled drugs.

The label is usually a gamma-emitting chemical, which may be attached to the drug particles or act as a surrogate for the drug. Because of difficulties in labeling drug particles directly, the surrogate approach is most commonly used. Regardless, it is key that the label mimic the behavior and not alter the characteristics of the inhaled therapeutic aerosol. With this technique, it is possible to measure total quantitative deposition or to describe relative regional deposition. The former is more difficult and requires careful accounting of the initial dose in the device and all sources of loss after inhalation, including exhaled radioactivity. Corrections must also be made for attenuation of radiation by superimposed body structures. Regional estimates of deposition are less problematic and have been described in terms of "central versus peripheral," "penetration index," "skew," and "kurtosis." One problem with two-dimensional scanning is that peripheral airways and alveoli overlay central airways and may cause errors in regional estimates. This error is greatly reduced by single photon emission computed tomography scanning.[47,48]

Can in vivo scintigraphic measurement of total or regional lung deposition predict clinical outcomes in patients? There is limited information on this subject, as most scintigraphic studies have not tied their results to a clinical outcome. Most of the available data involve inhaled bronchodilators in asthma patients. In one study, when similar doses of labeled albuterol were given to asthmatic subjects via nebulizer, MDI, or DPI, deposition amount was greater with the MDI than with the DPI or nebulizer (Table 1).[49] Forced expiratory volume in the first second (FEV_1) improvement was significantly greater for the MDI and was not related to the pattern of deposition. The importance of dose was also shown by Dolovich et al[50] in a study wherein equal doses of a bronchodilator were delivered to the lungs in either 0.5 μm or 2.4 μm particles. When cumulative dose to the lungs was matched, as measured by gamma camera images, the improvement in pulmonary function was the same for both particle sizes. Similarly, in a dose-response study of terbutaline deposited preferentially to the large or small airways in asthmatics, there was no difference in FEV_1 improvement.[51] In another study by Newman et al, scintigraphy measurements were used to explain differences in lung function improvement due to poor inhaler technique in asthmatic subjects (Fig. 5).[52]

Correlation of scintigraphic deposition measurements and clinical outcomes in patients is also important for therapeutic aerosols that require more specific targeting in the lungs, such as antibiotics, gene therapy, and drugs intended for systemic absorption. The antibiotic pentamidine is effective prophylaxis against the opportunistic pathogen *Pneumocystis carinii* that resides in the alveoli and causes pneumonia. Gamma scintigraphy has been very helpful in selecting delivery devices that preferentially deliver drug particles to the lung periphery, and use of these devices is associated with fewer adverse effects, such as cough.[53] It was thought that therapy failure could be related to differences in total dose or distribution of pentamidine, but this was investigated in patients with human immunodeficiency virus infection and was found not to be the case.[54,55] Another example is that of inhaled insulin, which was not very effective at lowering plasma glucose in early studies.[56] When attention was given to optimizing the dose delivered to the lungs, using scintigraphy studies, much greater efficacy was seen in diabetic subjects.[57] Although total dose of deposited insulin was not correlated with change in plasma glucose level, lower glucose level was significantly correlated to greater insulin deposition in the bases of the lungs.[58]

Scintigraphic measurements of radiolabeled drug deposition are invaluable for assessing drug delivery and the effects of differing particle sizes, drug formulations, delivery devices, breathing patterns, and lung diseases. These techniques give information that is not available by other means, and can help explain variability in clinical response and toxicity. They are also essential for targeting drug delivery to specific locations and optimizing efficacy. There are limited studies linking scintigraphy measurements to clinical outcomes in patients, and more emphasis should

Table 1. Lung Function Values and Scintigraphic Deposition Measurements in 9 Asthmatics Inhaling 400 μg Albuterol from Different Devices

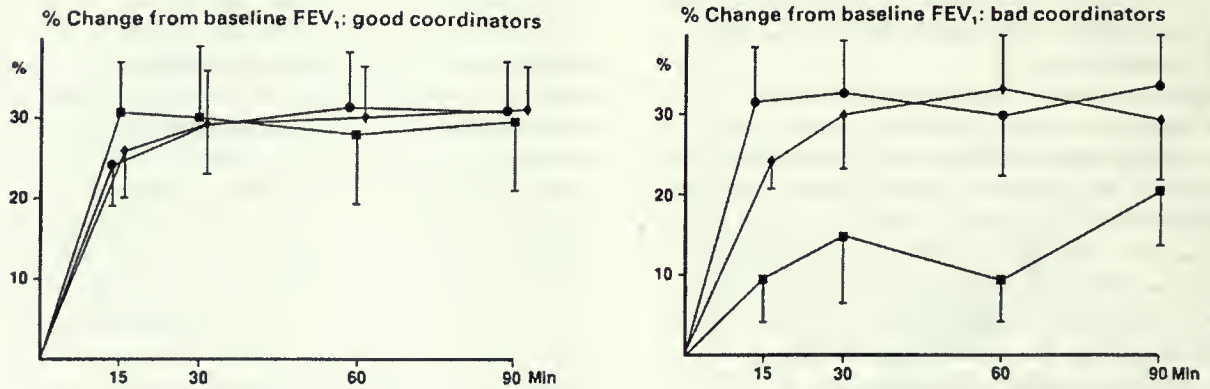
	Metered-Dose Inhaler	Dry Powder Inhaler	Nebulizer
Baseline FEV_1 (L)	1.4 ± 0.13	1.42 ± 0.13	1.43 ± 0.15
Baseline PEF (L/m)	246 ± 25	248 ± 27	246 ± 28
Total dose deposition (%)	11.2 ± 0.8*	9.1 ± 0.6	9.9 ± 0.7
Peripheral deposition (% of total)	16.1 ± 1.2	12.7 ± 1.3	24.5 ± 1.0
Improvement in FEV_1 (%)	35.6 ± 7.4†	25.2 ± 6.2	25.8 ± 6.5
Improvement in PEF (%)	40.1 ± 6.6	32.4 ± 6.7	29.9 ± 5.2

Values are means ± SEM.
FEV_1 = forced expiratory volume in the first second. PEF = peak expiratory flow.
*Significantly greater than dry powder inhaler ($p < 0.025$), but not nebulizer.
†Significantly greater than dry powder inhaler or nebulizer ($p < 0.025$).
(Modified from Reference 49.)

be put on this subject. Documentation of these relationships is necessary for optimizing dose and site of delivery, as well as for minimizing toxicity and expense.

Pharmacokinetics and Pharmacodynamics

Another approach to assessing respiratory drug delivery is to measure plasma levels of drug after absorption (pharmacokinetics) and to relate those levels to clinical efficacy and toxicity (pharmacodynamics). Determination of pharmacokinetic profiles is difficult for inhaled drugs because the plasma levels are very low, requiring a sensitive assay, and may be altered by drug absorbed from the GI tract. Much of the available pharmacokinetic data for inhaled drugs involves bronchodilators, often in doses much larger than customarily used in clinical care.[59] With new tech-



	Own MDI	Taught MDI	Autohaler
Good Coordinators	19%	13%	18%
Bad Coordinators	7%	23% *	21% *

Fig. 5. Comparison of scintigraphic lung deposition amounts (listed in table) and forced expiratory volume in the first second (FEV_1) in asthmatic subjects inhaling albuterol from a metered-dose inhaler. "Own MDI" (square symbols) was performed without instruction. "Taught MDI" (diamond symbols) was with instruction. Autohaler (circle symbols) was with a breath-actuated inhaler. Bad coordinators had significantly higher ($p < 0.01$) lung deposition with instruction or with the breath-actuated inhaler than without instruction, and this was reflected in greater improvement in FEV_1. (Modified from Reference 52, with permission.)

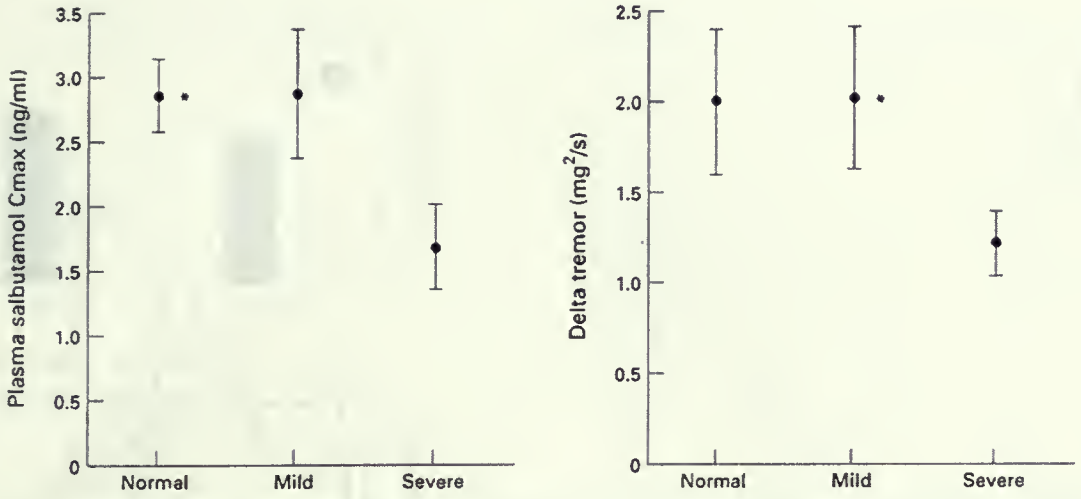


Fig. 6. Maximum albuterol plasma levels and change in tremor in normal, mildly asthmatic, and severely asthmatic subjects after inhaling nebulized albuterol. Severely asthmatic subjects had significantly lower albuterol levels and less tremor. There were no differences in forced expiratory volume in the first second response for the three groups. (From Reference 66, with permission.)

niques and more sensitive assays, evidence is accumulating that pharmacokinetic and pharmacodynamic measurements can be helpful for understanding drug absorption across the pulmonary vascular bed, as well as the therapeutic and adverse effects. Plasma levels and corresponding clinical outcomes can be used to verify predictions from in vitro models. One study compared two nebulizers in a dose response study of albuterol in asthmatics.[60] One of the nebulizers delivered a smaller particle size and greater mass output in preliminary studies, which would indicate a larger dose of drug delivered to the lungs. Plasma albuterol levels for this nebulizer were two-fold higher, with increased systemic β-2 responses. The pulmonary function improvements for the two nebulizers were similar, however. For albuterol, the plateau of the dose response curve is reached at low doses, and increased drug delivery may not achieve a greater lung function response. For the nebulizer with increased delivery in this study, it would be possible to decrease the amount of drug used, save money, and avoid toxicity. This example points to the need for more studies relating in vitro and in vivo measurements to clinical outcomes.

Information can be obtained from pharmacodynamic relationships that may not be explained by in vitro or scintigraphic predictions. For example, scintigraphic studies of albuterol inhaled from an MDI and a low-velocity pressurized device were compared, and showed similar lung deposition values, with the low-velocity device showing less oropharyngeal deposition.[61] When pharmacokinetic and dynamic studies were done, the low-velocity device was associated with significantly higher blood levels and associated systemic responses, such as raised heart rate and tremor.[62] These findings would not have been predicted by scintigraphy measurements. Caveats to these two studies are that: (1) the scintigraphy measurements were made in asthmatic subjects and the pharmacokinetic and pharmacodynamic measurements were made in healthy subjects, (2) the plasma levels were only measured after administration of a cumulative dose of 2,600 μg of albuterol, and (3) the systemic responses at commonly-used doses of albuterol were not clinically important. This example points out the need for well designed and controlled studies comparing in vivo outcomes. Ideally, comparisons should be done in the same study population, or, better yet, in the same subjects, using realistic doses of inhaled drugs.

Initial lung delivery and onset of action of β-2 agonists can be examined by measuring plasma levels over the 20–30-minute interval following inhalation. This approach has been used in normal subjects to compare generic and brand name preparations of albuterol,[63] to compare different spacer devices,[64] and to show differences in lung uptake and toxicity for the same dose (1,200 μg) of albuterol given by different devices.[65] When this type of measurement was applied in asthmatics, those with more severe airway obstruction showed significantly lower albuterol concentrations in the first 30 minutes after inhalation than did mildly asthmatic and normal subjects (Fig. 6).[66] The asthmatic subjects also had attenuated responses in tremor, heart rate, and the middle half of forced expiratory flow (FEF_{25-75}), but absolute FEV_1 changes were similar to those in the mildly asthmatic subjects.

In order to quantitate lung dose and determine full pharmacokinetic profiles, it is necessary to use a sensitive assay and eliminate the contribution of drug that is absorbed from the oropharynx and GI tract after swallowing. One approach involves oral administration of slurries of acti-

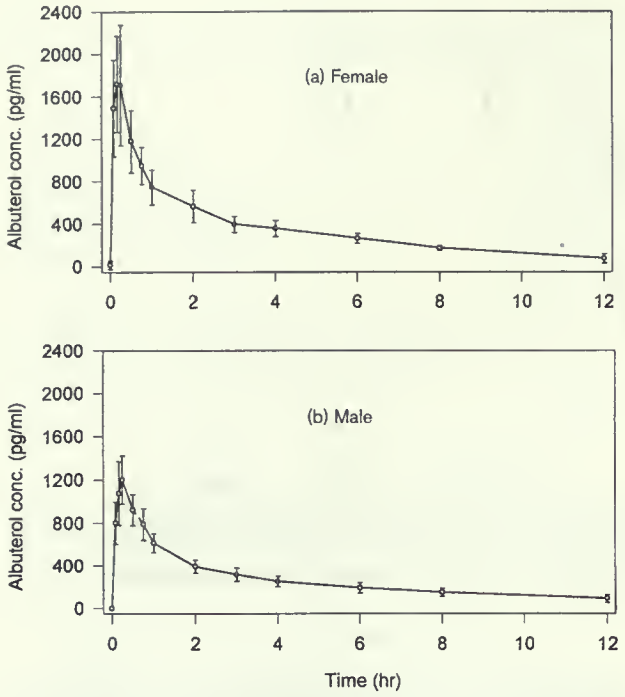


Fig. 7. Effect of gender on pharmacokinetics in normal subjects inhaling 180 μg of albuterol from a metered-dose inhaler with spacer. Female subjects achieved peak concentrations more rapidly and had higher mean peak concentration than male subjects. (From Reference 67, with permission.)

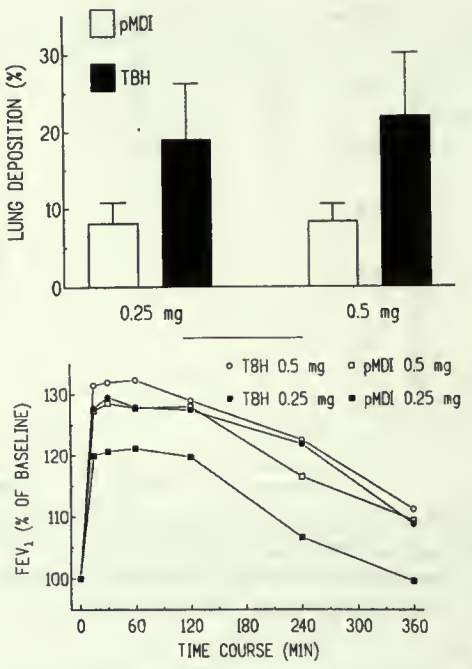


Fig. 8. Comparison of lung deposition of two doses of terbutaline measured by charcoal block method with change in forced expiratory volume in the first second (FEV_1) for asthmatic subjects using a pressurized metered-dose inhaler (pMDI) or a Turbuhaler dry powder inhaler (TBH). At the lower dose, the Turbuhaler deposited about twice as much drug in the lungs and caused a greater improvement in FEV_1 than the metered-dose inhaler. At the higher dose, the improvement in FEV_1 was the same for both inhalers. (Modified from Reference 68, with permission.)

vated charcoal to absorb the drug in the mouth and GI tract, so that plasma levels of drug reflect that absorbed from the lungs. When healthy subjects were given 180 μg of albuterol via MDI with spacer, peak drug levels in plasma were reached in 12 minutes and the half-life of elimination was around 4 hours.[67] There were gender differences, with female subjects having higher peak values and reaching peak concentrations more rapidly than males (Fig. 7). An alternative way of looking at lung dose of drug is to measure urinary drug excretion over 36–48 hours in combination with charcoal block. This works well for drugs that are not metabolized in the airways or in the lungs. Deposition measurements using this technique have been compared to gamma scintigraphy using a terbutaline DPI in healthy subjects, and scintigraphy was found to give slightly higher deposition values (27% vs 21%).[68] Borgström et al used charcoal block and urine studies to measure differences in lung deposition between an MDI and a DPI in asthmatics.[69] Spirometric testing showed that at the lower dose of terbutaline, improvement in FEV_1 was significantly greater for the device that showed greater lung deposition, but that at the higher dose there was no difference in FEV_1, despite the higher deposition (Fig. 8). Once again, clinical assessments show that higher deposition amounts of bronchodilators may not improve the clinical outcome and may cause toxicity.

Another group of investigators has used the percentage recovery of albuterol in urine 30 minutes post inhalation as an index of the relative bioavailability of albuterol to the lungs.[70] This methodology does not measure total lung dose, but is noninvasive, avoids the administration of charcoal, and is a useful tool for comparisons. The technique has been used to measure the effect on drug delivery of DPIs,[71] spacers,[72] and inhaler techniques.[73] Most of these studies were done in healthy subjects and did not involve measurement of pulmonary or systemic effects. One study[71] included asthmatic patients and pulmonary function data showing significantly greater relative lung bioavailability with the DPI than with the MDI, but no difference in the postbronchodilator pulmonary function data. Other investigators have used overnight urinary albuterol excretion as an assessment of nebulized albuterol delivery in chronic obstructive pulmonary disease (COPD) patients.[74]

Less information is available about the pharmacokinetics and pharmacodynamics of inhaled steroids. Many steroids, such as budesonide and fluticasone, have a high degree of first-pass hepatic metabolism of the gastrointestinally absorbed drug, so that lung absorption is a major determinant of systemic bioavailability.[75] This has important implications for systemic toxicity and the risk-benefit

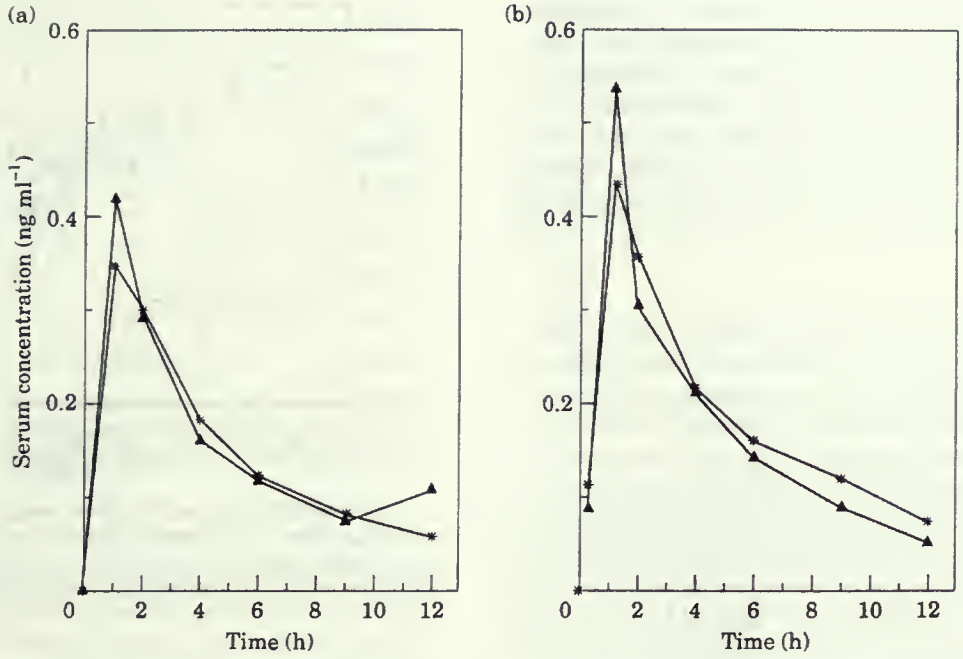


Fig. 9. Pharmacokinetic profiles for beclomethasone with hydrofluoroalkane (HFA) propellant (triangles) versus chlorofluorocarbon (CFC) propellant (asterisk). The beclomethasone dose with HFA propellant is half of that with the CFC-propelled formulation (200 μg vs 400 μg), but, because of a greater fine particle fraction, results in similar blood levels of drug. Panel (a) shows serum profiles after one dose. Panel (b) shows steady state after 14 days. (From Reference 77, with permission.)

ratio of high doses of inhaled steroids. Studies done in children showed about 20% of total systemic availability of budesonide delivered by Turbuhaler is from orally deposited drug.[76] Reformulation of beclomethasone dipropionate with the chlorofluorocarbon (CFC)-free propellant hydrofluoroalkane-134a (HFA) produces an aerosol with a greater total mass of fine drug particles than the CFC-propelled preparation.[77] This has stimulated interest in documenting the effect of the change in particle size characteristics on pharmacokinetics and efficacy/toxicity profiles. Pharmacokinetic variables for HFA-propelled beclomethasone were similar to those obtained with approximately twice the dose of the CFC preparation (Fig. 9). The greater systemic bioavailability of HFA-propelled beclomethasone did not cause increased systemic toxicity, however. Adrenal effects were found to be comparable to the CFC formulation at the same dose.[78]

There is increasing interest in documenting the pharmacokinetic and pharmacodynamic profiles of inhaled drugs. These measurements can provide confirmation of in vitro and scintigraphic assessments and can often add insights into the relationship between drug delivery and clinical efficacy and toxicity. In many cases, it is important to distinguish the relative contributions of lung and GI tract absorption. More studies are needed to correlate in vitro and in vivo measurements of inhaled drugs with pharmacokinetics/dynamics in patient populations. This type of study would form a very strong foundation for optimal design of long-term clinical trials.

Clinical Outcomes

There is no substitute for measures of clinical outcomes of inhaled drug delivery; all theoretical predictions and in vitro and in vivo measurements form the foundation for clinical trials in patients. Overall, there is a lack of published, well designed, randomized, controlled trials addressing inhaled drug delivery. There is also a lack of trials comparing in vitro and in vivo predictions of lung dose of drug with clinical outcomes. At this level of investigation, intersubject variability in disease, performance and adherence also come into play. A variety of clinical outcomes have been used, ranging from objective to subjective in nature. The "best" outcome involves a value judgment, and may vary according to the perspective of the observer. The outcomes will also vary with the nature of the inhaled drugs and diseases. Most of the material presented here pertains to inhaled bronchodilators and steroids in both asthma and COPD. The most commonly used outcomes in these types of trials will be discussed, with some examples from the clinical trials literature. Criteria of a valid outcome measure are that it must be: (1) appropriate to the question to be answered, (2) precise, (3) complete, and (4) not influenced by the process of observation.[79] It is also

helpful if the outcome measure is noninvasive and inexpensive. The ultimate outcomes are mortality and morbidity, but these are rarely available in clinical assessments of inhaled drugs. The most frequently used clinical outcome measures are intermediate ones, and the effect on morbidity and mortality is inferred. In the final analysis, the best outcomes must in some way be important to the patient.

Spirometry

Lung function testing is one of the cornerstones of evaluating therapy for airway obstruction.[80] Most studies of inhaled bronchodilators and steroids monitor improvement in spirometry, particularly FEV_1, over time. Studies of β-2 agonists and anticholinergics are usually short-term and involve fewer subjects, since immediate effects can be monitored. Although the documentation of a bronchodilator response seems straightforward and objective, the means of expressing the response, the reproducibility and the predictive value of this test are suboptimal. The current American Thoracic Society statement recommends that a positive response requires at least a 12% increment in baseline FEV_1 or forced vital capacity, and a 200 mL increase.[81] Expressing improvement in FEV_1 as a percent of baseline is problematic in that it is very dependent on the prebronchodilator lung function, and has poor reproducibility.[82] When expressed as percentage change, a given absolute change in FEV_1 appears much larger for lower baseline values, and the criterion of 12–15% improvement from baseline selects the most obstructed subjects. This "regression toward the mean" may be more problematic in trials with COPD subjects. Some authors have advocated expressing response as absolute change or percent of the predicted FEV_1.[83,84] Another measure used in clinical trials is the area under the FEV_1 versus time curve for expression of response to a single dose, but there is little information about reproducibility. Even when using different expressions of the bronchodilator response, repeated studies show poor reproducibility. When 6 measurements were done over 24 months, the coefficient of variation was from 34–50% in asthma to 46–61% in COPD.[82] Another investigation in COPD patients showed very poor reproducibility in bronchodilator response over time (Fig. 10).[85]

Bronchodilator response may not be related to symptomatic response to therapy. Significant improvements in severity of dyspnea and exercise tolerance may occur in the absence of a bronchodilator response.[85] Also, patients who do not manifest acute reversibility with albuterol may benefit from long-term treatment with β-2 agonists.[86] It is possible that a response to bronchodilator may be reflected in physiologic tests other than FEV_1. One study found that in about 15% of patients with reversible disease, a bronchodilator response was detectable only via volume-related indices measured by body plethysmography.[87] Other

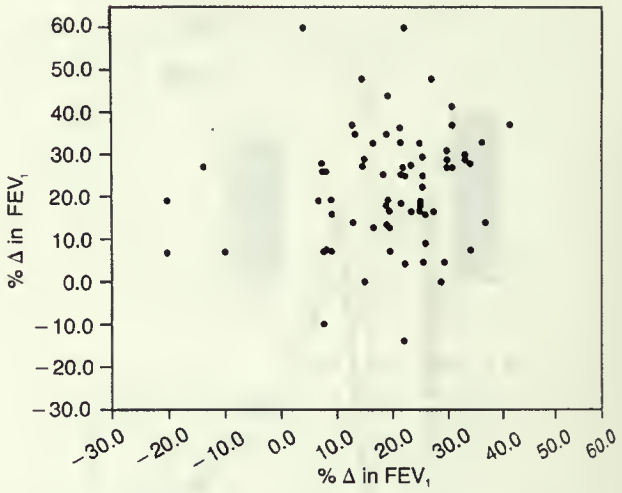


Fig. 10. Reproducibility of bronchodilator response in 24 patients with chronic obstructive pulmonary disease. Each subject had three measurements over a several-week period. No significant relationship was found. (From Reference 85, with permission.)

investigators found increases in maximal flow and changes in inspiratory capacity that were not detected by changes in FEV_1.[88] These factors may explain why some patients improve subjectively with bronchodilators but show no spirometric improvement.

Another issue pertinent to bronchodilator response is the relative dose.[75] As noted previously in this paper, the plateau of the dose response relationship is rapidly reached with increasing doses of bronchodilators. This relationship has been described in asthmatic patients for bronchodilator medications and also for the same medication in different devices.[89–92] When comparing drug delivery from different devices, it is important to give equipotent doses and to avoid doses on the plateau of the dose-response curve. Dose-response relationships can be established in the study population to aid dose selection prior to the clinical trial (Fig. 11).[93] By assessing responses on the steep part of the dose-response curve, for example, a DPI formulation of albuterol achieves equivalent spirometric response in asthmatics at half the dose of an MDI.[94] Only studies that incorporate a dose-response comparison and are able to show within-delivery-method dose-response differences have the internal sensitivity to assure that errors are not being made when comparing different delivery methods. In contrast to most bronchodilators, dose-response relationships are more critical for expensive or toxic drugs with narrow therapeutic ranges.

Studies of inhaled steroids require monitoring lung function over a much longer period of time (weeks or months), since they rarely produce a measurable short-term effect, and involve larger samples. Like bronchodilators, there are problems with methods of expressing change in spirometry and with reproducibility over time. Dose-response re-

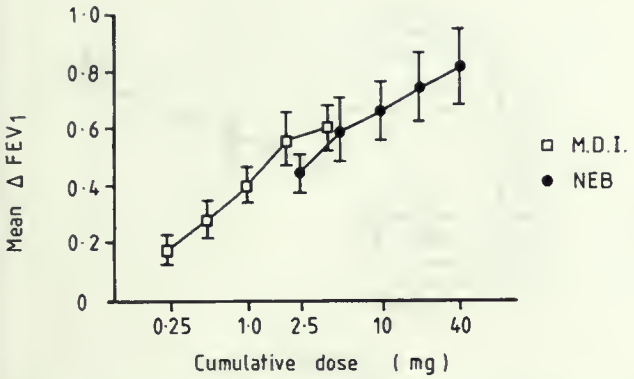


Fig. 11. Example of dose-response relationship for terbutaline administered by two different devices in patients with asthma and chronic obstructive pulmonary disease. (From Reference 93, with permission.)

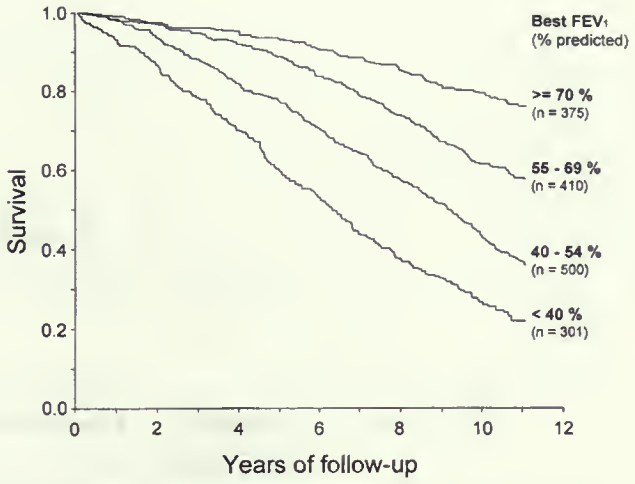


Fig. 12. Relationship of best forced expiratory volume in the first second (FEV_1) to survival in 1,586 subjects with asthma or chronic obstructive pulmonary disease. Reversibility of FEV_1 to bronchodilators or corticosteroids contributes to survival prediction only to the extent that it modifies FEV_1, and was not an independent predictor of survival. (From Reference 95, with permission.)

lationships are even more important for inhaled steroids, as greater pharmacologic potency does not always translate into greater clinical efficacy, but can cause greater systemic toxicity.[75]

Are FEV_1 and bronchodilator response valid outcome measures in terms of ultimate prognosis or mortality? When this was examined in both asthma and COPD patients, bronchodilator and corticosteroid reversibility both contributed to survival prediction to the extent that they modified FEV_1.[95] Reversibility per se did not influence survival. Achieving the best possible lung function, however, does affect survival in asthma and COPD and is a desirable goal for inhaled drug therapy (Fig. 12). FEV_1 is an objective measurement and remains a mainstay of assessment when comparing different inhaled drugs, formulations, or devices.[96] In spite of this, interpretation of spirometric outcomes, whether to assess response to bronchodilators or corticosteroids, is fraught with difficulties. When comparing results among trials, careful attention should be given to the definition of the population, reversibility criteria, method of calculating response, and the dose-response relationship.

Peak Expiratory Flow

Peak expiratory flow (PEF) diaries are commonly used in clinical trials of asthma subjects for outpatient monitoring. The relative importance of PEF monitoring to the efficacy of asthma intervention is not clear,[97] and there is variability in correlation with spirometry as well as variability among different brands of meters.[98] Timing of prior bronchodilator use can affect the readings and impart bias to outpatient monitoring for clinical trials.[99] It is not clear whether PEF changes are predictive of asthma exacerbations. In a study with inhaled corticosteroids in children, PEF variation showed poor correlation with changes in other measures of asthma severity, such as symptoms, spirometry, and bronchoprovocation.[100] Another study monitored changes in symptoms and PEF prior to exacerbations, and found that exacerbations identified by the need for oral corticosteroids were associated with more symptoms and smaller changes in PEF.[101] PEF monitoring is advantageous in that it is one of the few objective measures available for following subjects as outpatients during clinical trials. It should be used in conjunction with, and never as a substitute for, spirometry and other lung function measures.

Bronchoprovocation

Bronchoprovocation testing is another way to assess respiratory drug delivery, primarily in asthmatic subjects. The ability of inhaled drugs to protect against increased airways responsiveness to a variety of stimuli can be measured in a dose-response fashion. This type of approach has been used to assess efficacy of bronchodilators and steroids, with the inference that a drug will protect against environmental triggers if proven to do so in laboratory studies.[102–104] Care must be taken in interpreting results, as there are numerous provoking agents and methods of measuring and expressing response. Bronchoprovocation can also be used to compare relative efficacy of delivery devices. Histamine bronchoprovocation has been used as a bioassay to compare albuterol delivered via MDI versus via nebulizer, in a dose-response fashion (Fig. 13).[105] Bronchoconstrictor responsiveness has sometimes been considered the opposite of bronchodilator responsiveness, but

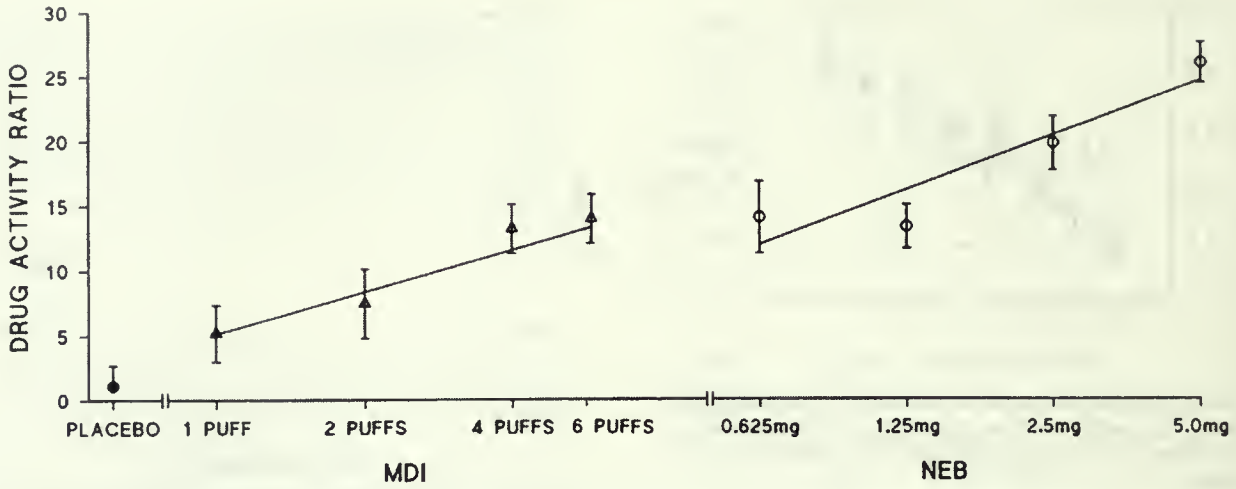


Fig. 13. Use of bronchoprovocation to test the efficacy of inhaled albuterol for protection against airway hyperresponsiveness in asthmatic subjects. Drug activity ratio is the ratio of the concentration of histamine required to decrease forced expiratory volume in the first second (FEV_1) by 20% (PC_{20}) after albuterol to that before albuterol. This method was used to compare doses of albuterol from different delivery devices. (From Reference 105, with permission.)

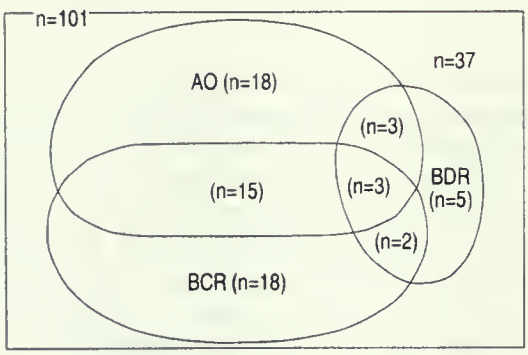


Fig. 14. Relationships between bronchodilator response (BDR), bronchoconstrictor response (BCR), and airway obstruction (AO) in a population-based study of 101 subjects. (From Reference 106, with permission.)

this may not be the case. Douma et al compared bronchoconstrictor and bronchodilator responses in a population-based study of 101 subjects and found the two not highly correlated, even in subjects with airway obstruction (Fig. 14).[106]

Is airway hyperresponsiveness a valid outcome for predicting long-term asthma control? When a treatment strategy aimed at reducing airway hyperresponsiveness was instituted in a large, multicenter trial, it resulted in more effective control of asthma and greater improvement of chronic airways inflammation, as measured by bronchial biopsy over a two-year period.[107] This was manifested by improvements in FEV_1 and fewer exacerbations. These findings indicate that additional information may be gained by assessing airway hyperresponsiveness that is not available from spirometry, bronchodilator studies, or symptoms. Bronchoprovocation testing may yield a better measure of the inflammatory state of the airways that can be used to gauge the level of inhaled corticosteroids required. Improved therapy will have an impact on important outcomes such as exacerbation rate. This is a controversial subject, however, and the relationship between the magnitude of airway inflammation and hyperresponsiveness has yet to be clarified.

Markers of Inflammation

In addition to assessing airway hyperresponsiveness, it is possible to measure cellular markers or mediators of inflammation in asthma.[108] These include eosinophils, eosinophilic cationic protein, histamine, leukotrienes, platelet activating factor, cytokines, chemokines, and nitric oxide. There is a growing amount of research using airway biopsies, bronchoalveolar lavage fluid, sputum, and exhaled gases, with the ultimate goal of establishing a link between markers of inflammation and functional changes in asthma. Over time, these cells and mediators are thought to cause airway remodeling and irreversible airway obstruction. In a study by Crimi et al, with asthmatic subjects, baseline FEV_1 was inversely related to number of eosinophils in sputum or bronchoalveolar lavage fluid, but there was no correlation between methacholine responsiveness and the number of inflammatory cells.[109] Other authors have shown a positive relationship between markers of inflammation and airway responsiveness.[110–111] Nonetheless, markers of inflammation do change in response to inhaled steroid therapy and may serve as a guide for determining optimal dose.[112–113] Using easily-obtained markers of inflammation in asthma, such as number of sputum eosinophils, may be a promising means of moni-

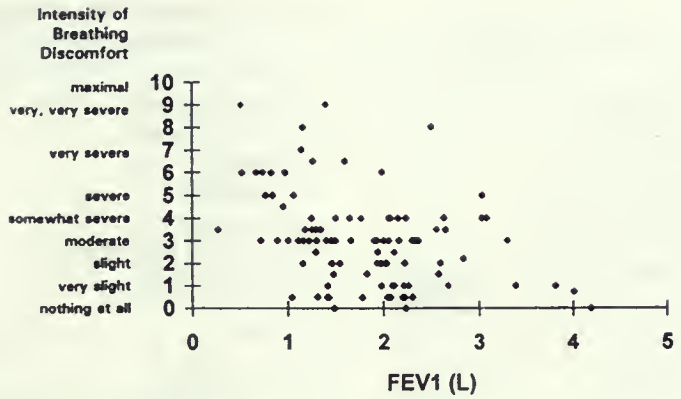


Fig. 15. Relationship between dyspnea, as measured by the Borg scale, and forced expiratory volume in the first second (FEV_1) for 25 asthmatic subjects undergoing bronchodilator therapy in the emergency department. The relationship was significant ($p < 0.0001$), but the correlation was not high ($r = -0.38$). (From Reference 120, with permission.)

toring therapy with inhaled steroids. This requires further studies in a larger population and correlation with other clinical outcomes such as exacerbation rate, hospitalizations, medication use, and symptoms.

Concomitant Care

It is important to document clinically relevant outcomes during trials of inhaled drug therapy in asthma and COPD. These include concomitant medication use, exacerbation rates, emergency department visits, hospital days, oral steroid use, and days missed from work or school. Such outcomes are directly related to morbidity and, possibly, to mortality, and have great impact on utilization of resources and patient quality of life. Unfortunately, these outcomes are difficult to document in small laboratory-based studies comparing delivery of different drug formulations or devices, as they require large study populations and long follow-up periods. Larger multicenter trials of new inhaled drug preparations or devices, sponsored by industry, are more likely to monitor these variables, and information may also be available through evidence-based medicine reviews of the available literature. An example is the Cochrane Database review of comparisons of β agonists delivered to asthma patients via nebulizer versus via MDI with holding chamber.[114] Twelve combined trials in adults and children showed that the MDI with holding chamber reduced time in the emergency room, but that hospitalization rates did not differ for the two delivery methods.

The most commonly reported type of concomitant care in long-term clinical comparisons of inhaled drug delivery is concomitant drug use (most often, β-2 agonist use).[93,94] Other comparative trials have documented exacerbation rates in asthma,[115–116] or have followed inhaled steroid use.[117] In general, published studies comparing different inhaled drug delivery strategies involve small numbers and short time periods, with pulmonary function testing as the primary outcome. There is a need for larger, long-term studies that include clinically and economically important outcomes such as concomitant medications and medical care.

Symptoms

Subjective outcomes are also important in gauging the efficacy of inhaled drugs. The perception of level of dyspnea, chest tightness, wheezing, cough, sputum, and activity level are probably of more concern to the patient than the more objective measurements of pulmonary function. These symptoms are also critical to day-to-day quality of life and are more likely to trigger medication use and visits to the physician or emergency department. In clinical trials, symptoms are usually monitored and scored in a structured way, using diaries. Dyspnea can also be quantified, most commonly with a Borg rating.[118] Several studies have shown that dyspnea is not closely related to objective measures of pulmonary function, and this lack of correlation may be more marked in COPD patients than in asthma patients. When Borg score was compared to prebronchodilator and postbronchodilator spirometry in COPD patients, there was no correlation.[119] Similarly, when Borg score was compared to FEV_1 in asthmatics during treatment in the emergency department, there was a significant relationship, but the correlation was low ($r = -0.38$) (Fig. 15).[120] In moderately to severely asthmatic subjects recording symptoms and PEF on an outpatient basis, there was only a weak association between change in symptoms and change in PEF.[121] In a large, random population sample undergoing histamine challenge test, the level of and increase in Borg score were not related to the level of and change in FEV_1.[122] In this study, an increase in Borg score

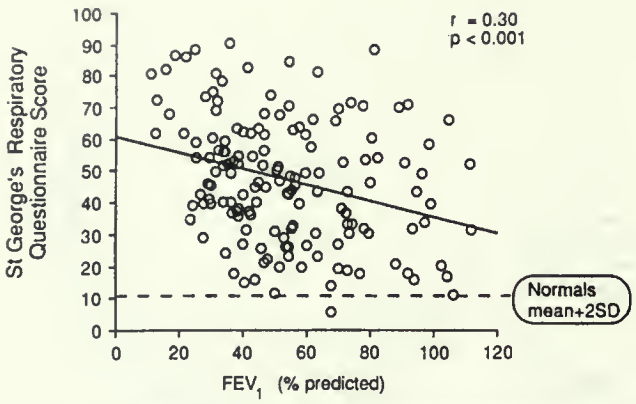


Fig. 16. Relationship between quality of life, as measured by the St George's Respiratory Questionnaire score, and postbronchodilator forced expiratory volume in the first second (FEV_1) in patients with chronic obstructive pulmonary disease. A high questionnaire score indicates worse quality of life. (From Reference 124, with permission.)

was associated with younger age, more severe airway responsiveness, atopy, and female gender. It is possible that objective tests other than FEV_1 or PEF have a better correlation with symptoms. In a study of COPD patients, increased inspiratory capacity was the best predictor of improvement in dyspnea and exercise endurance after ipratropium bromide.[123]

Quality of Life

Quality of life or health status assessment is a means of quantifying the impact of disease on daily life and well being, and can be used to gauge the impact of clinical interventions.[124] This is done in a standardized fashion by using questionnaires that address symptoms, activities, and emotions. These questionnaires are being used more often in clinical trials, and provide information not available with traditional physiologic measurements. Questionnaires have been developed for COPD and asthma and have been validated in these populations.[125–127] Health status scores appear to be reproducible and are correlated, although weakly, with other measures of disease, such as FEV_1 (Fig. 16).[124] In spite of this, it is important to monitor effects of disease and therapy on day-to-day life. We also know that no single test of lung function can assess the disturbances in airway obstruction. It is possible to have a marked improvement in health status score with only a small improvement in pulmonary function. In a study in asthmatic subjects, an asthma-specific quality of life questionnaire was used to measure the effect of salmeterol, compared to albuterol or placebo.[128] Quality of life was significantly better with salmeterol than with albuterol or placebo. There were also significant, although modest, correlations with other clinical outcomes (Table 2). Although the tendency of many physicians is to look preferentially at objective measures, what patients tell us about the impact of disease on daily life is an important and valid outcome measure. Quality of life studies help place in perspective the importance to the patient of the improvement in pulmonary function and symptoms produced by therapeutic aerosols.

Table 2. Longitudinal Correlations Between Quality of Life and Clinical Outcomes

Change in Clinical Outcomes	Change in Overall Quality of Life	Change in Symptoms
Morning PEF	0.58	0.60
Evening PEF	0.48	0.50
Morning symptoms	0.47	0.49
Nights without sleep disturbance	0.28	0.30
Daytime symptoms	0.54	0.52
FEV_1	0.38	0.36
Albuterol use	0.43	0.41

PEF = peak expiratory flow
FEV_1 = forced expiratory volume in the first second
All correlations are significant ($p < 0.001$).
(Modified from Reference 128.)

Toxicity

No discussion of clinical outcomes would be complete without mention of adverse effects or toxicity. Monitoring of toxicity is crucial for determination of the risk/benefit ratio and optimal dose. Both clinical efficacy and toxicity depend on the lung deposition and bioavailability of drug, as well as the dose-response relationship.[75] Enhanced absorption from the lung, due to either a larger dose or altered anatomic distribution, may also increase systemic toxicity. Types of adverse effects vary among inhaled drugs and may be local or systemic. Typical systemic toxic effects of β-2 agonists are tremor, hypokalemia, and tachycardia; examples have been given in earlier sections about the relationship to efficacy and plasma drug levels.[60,62,66] In general, for β-2 agonists, the plateau of clinical response is reached before there is substantial systemic toxicity.

There has been much more concern about short-term and long-term adverse effects of inhaled corticosteroids.[129] Local toxicity is caused by oropharyngeal deposition and can cause thrush, cough, and hoarseness. Systemic toxicity includes adrenal suppression, skin thinning, and effects on bone metabolism. Most commonly, studies have monitored morning cortisol levels or the more sensitive measure of 24-hour urinary cortisol.[75] Lung bioavailability is a

Table 3. Pros and Cons of In Vitro Predictions, In Vivo Measurements, and Clinical Outcomes

	Pro	Con
In vitro predictions	Good for quality control and comparisons Can be done without human subjects Good for troubleshooting and testing clinical design	Does not measure clinical efficacy or toxicity Does not account for effect of lung disease Tends to overestimate lung deposition
Scintigraphic measurements	Measures site and amount of deposition Does assess effect of lung disease Useful for drug targeting	Requires human subjects Exposure to radiation Does not measure clinical efficacy or toxicity
Pharmacokinetics and pharmacodynamics	May explain relationship between drug delivery and efficacy/toxicity Confirmation of in vitro and scintigraphic findings Important for systemic drug efficacy and toxicity	Invasive May need to block gastrointestinal absorption Expensive assays
Spirometry	Objective Commonly done in clinical medicine Inexpensive Absolute FEV_1 is related to survival	Poor reproducibility Not highly correlated with symptoms May not predict long-term response Best expression of response is controversial Affected by dose-response relationship
Peak expiratory flow	Objective Portable devices Can be used for outpatient monitoring	Variability among brands Affected by timing of bronchodilator use May not predict exacerbation Not correlated with other measures
Bronchoprovocation	May be a better index of airway inflammation and asthma control Use as outcome may have more impact on exacerbations Can be used to dose inhaled steroids	Lacks standardization Requires special drug and equipment Not correlated with bronchodilator response
Markers of inflammation	Respond to inhaled steroid therapy and may be better index of asthma control	May require invasive tests Relationship to airway responsiveness not clear Predictive value not clear
Concomitant care	Clinically relevant Related to morbidity, mortality, and costs	Requires long-term follow-up and large populations
Symptoms	Important to quality of life More likely to trigger medication use and doctor visits	Subjective Weak correlations with objective measures
Quality of life	Quantifies impact of disease and therapy on daily life Patient-important outcome Reproducible and validated	Subjective Modest correlations with objective measures

FEV_1 = forced expiratory volume in the first second.

primary determinant of systemic toxicity of inhaled steroids, because of first-pass metabolism, and this varies with preparation. In general, doses up to 1,000 μg are safe, and there is a linear dose response. Above 1,000 μg there may be a plateau in response and increased toxicity. Fluticasone appears to have more systemic toxicity than budesonide at these doses.[130]

Summary

There is no "best" outcome or "gold standard" in the assessment of inhaled drug delivery. All levels of inquiry are important in development of drug formulations and delivery devices, and culminate in optimal therapy for the patient. Some advantages and disadvantages of each ap-

proach are summarized in Table 3. Each level forms a framework for the next step in the process, with in vitro leading to in vivo, followed by clinical trials. For optimal design, predictions and measurements of inhaled drug delivery should be done prior to large, expensive clinical trials. Bench testing with in vitro models is essential to document the performance of the delivery device/drug combination, whereas in vivo studies examine the behavior of the aerosol in human subjects. Both scintigraphy and pharmacokinetic/pharmacodynamic studies can add insights into the relationship between drug delivery and clinical efficacy and toxicity.

There is a need for continued investigation on the subject of inhaled drug delivery, including more trials that bridge the levels of testing. We need more trials comparing in vitro with in vivo outcomes, as well as trials that relate in vivo assessments to clinical outcomes. In the final analysis, however, there is no substitute for clinical trials in patients. There is a lack of published, well-designed, randomized, controlled clinical trials comparing delivery devices or drug formulations. For these, attention must be given to the definition of the population, the dose-response relationships, and the expression of the physiologic responses. It is also important that clinical trials monitor both objective and subjective outcomes, as symptoms and quality of life measures help quantify the impact of disease and therapy on daily life.

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REFERENCES

1. Bates DV, Fish BR. Deposition and retention models for internal dosimetry of the human respiratory tract. Task Group on Lung Dynamics. Health Phys 1966;12:173–208.
2. Phelan RF, Cuddihy FG, Fisher GL, Moss OR, Schlesinger RB, Swift DL, Yeh H-C. Main features of the proposed NCRP respiratory tract model. Rad Prot Dos 1991;38:179–184.
3. Bair WJ. Overview of ICRP respiratory tract model. Rad Prot Dos 1991;38:147–152.
4. Phalen RF, Oldham MJ, Kleinman MT, Crocker TT. Tracheobronchial deposition predictions for infants, children and adolescents. In: Dodgson J, McCallum RI, Bailey MR, Fisher DR, editors. Inhaled particles VI. Oxford: Pergamon Press; 1988: 11–21.
5. Hofmann W. Modeling techniques for inhaled particle deposition: the state of the art (review). J Aerosol Med 1996;9(3):369–388.
6. Heyder J, Gebhart J, Rudolf G, Schiller CF, Stahlhofen W. Deposition of particles in the human respiratory tract in the size range 0.0005–15 μm. J Aerosol Sci 1986;17:811–825.
7. Martonen TB, Katz IM. Deposition patterns of aerosolized drugs within human lungs: effects of ventilatory parameters. Pharm Res 1993;10(6):871–878.
8. Ferron GA, Oberdörster G, Henneberg R. Estimation of the deposition of aerosolized drugs in the human respiratory tract due to hygroscopic growth. J Acrosol Med 1989;2:271–284.
9. Martonen TB, Katz I. Deposition patterns of polydisperse aerosols within human lungs. J Aerosol Med 1993;6:251–274.
10. Martonen TB. Mathematical model for the selective deposition of inhaled pharmaceuticals. J Pharm Sci 1993;82(12):1191–1199.
11. Kim CS, Kang TC. Comparative measurement of lung deposition of inhaled fine particles in normal subjects and patients with obstructive airway disease. Am J Respir Crit Care Med 1997;155(3): 899–905.
12. Anderson PJ, Blanchard JD, Brain JD, Feldman HA, McNamara JJ, Heyder J. Effect of cystic fibrosis on inhaled aerosol boluses. Am Rev Respir Dis 1989;140(5):1317–1324.
13. O'Riordan TG, Walser L, Smaldone GC. Changing patterns of aerosol deposition during methacholine bronchoprovocation. Chest 1993;103(5):1385–1389.
14. Howite JS, Gorvoy JD, Smaldone GC. Quantitative deposition of aerosolized gentamicin in cystic fibrosis. Am Rev Respir Dis 1987; 136(6):1445–1449.
15. Anderson PJ, Wilson JD, Hiller FC. Respiratory tract deposition of ultrafine particles in subjects with obstructive or restrictive lung disease. Chest 1990;97(5):1115–1120.
16. Kim CS, Brown LK, Lewars GG, Sackner MA. Deposition of aerosol particles and flow resistance in mathematical and experimental airway models. J Appl Physiol 1983;55(1 Pt 1):154–163.
17. Gonda I. Targeting by deposition. In: Hickey AJ, editor. Pharmaceutical aerosol inhalation technology. New York: Marcel Decker; 1992: 61–82.
18. Kim CS, Eldridge MA, Sackner MA. Oropharyngeal deposition and delivery aspects of metered-dose inhaler aerosols. Am Rev Respir Dis 1987;135(1):157–164.
19. Smith EC, Denyer J, Kendrick AH. Comparison of twenty three nebulizer/compressor combinations for domiciliary use. Eur Respir J 1995;8(7):1214–1221.
20. Alvine GF, Rodgers P, Fitzsimmons KM, Ahrens RC. Disposable jet nebulizers: how reliable are they? Chest 1992;101(2):316–319.
21. Wilson AF, Mukai DS, Ahdout JJ. Effect of canister temperature on performance of metered-dose inhalers. Am Rev Respir Dis 1991; 143(5 Pt 1):1034–1037.
22. Coates AL, MacNeish CF, Meisner D, Kelemen S, Thibert R, MacDonald J, Vadas E. The choice of jet nebulizer, nebulizing flow, and addition of albuterol affects the output of tobramycin aerosols. Chest 1997;111(5):1206–1212.
23. Dennis JH, Hendrick DJ. Design characteristics for drug nebulizers. J Med Eng Technol 1992;16(2):63–68.
24. O'Doherty MJ, Miller RF. Aerosols for therapy and diagnosis (review). Eur J Nucl Med 1993;20(12):1201–1213.
25. Clark AR, Gonda I, Newhouse MT. Towards meaningful laboratory tests for evaluation of pharmaceutical aerosols. J Aerosol Med 1998;11 Suppl 1:S1–S7.
26. Dennis JH. A review of issues relating to nebulizer standards. J Aerosol Med 1998;11 Suppl 1:S73–79.
27. Adams WP, Poochikian G, Taylor AS, Patel RM, Burke GP, Williams RL. Regulatory aspects of modifications to innovator bronchodilator metered dose inhalers and development of generic substitutes (review). J Aerosol Med 1994;7(2):119–134.
28. Van Oort M. In vitro testing of dry powder inhalers. Aerosol Sci Technol 1995;22:364–373.
29. US Department of Health and Human Services, Food and Drug Administration. Center for Drug Evaluation and Research. Guidance for industry: metered dose inhaler (MDI) and dry powder inhaler (DPI) drug products (Draft). Oct, 1998.
30. Laube BL, Jashnani R, Dalby RN. Predicting in vivo lung deposition of cromolyn sodium from in vitro estimates. J Aerosol Med 1998;11 Suppl 1:S35–S42.

31. Newman SP. How well do in vitro particle size measurements predict drug delivery in vivo? J Aerosol Med 1998;11 Suppl 1:S97–S104.
32. Olsson B, Asking L, Borgström L, Bondesson E. Effect of inlet throat on the correlation between measured fine particle dose and lung deposition. In: Dalby RN, Byron PR, Farr SY, editors. Respiratory drug delivery V. Buffalo Grove IL: Interpharm Press; 1996: 273–281.
33. Velasques DJ, Gabrio B. Metered dose inhaler aerosol deposition in a model of the human respiratory system and a comparison with clinical deposition studies. J Aerosol Med 1998;11 Suppl 1:S23–S28.
34. Leach CL. Relevance of radiolabeled steroid inhalation studies to clinical outcomes. J Aerosol Med 1998;11 Suppl 1:S29–S34.
35. Smaldone GC, Fuhrer J, Steigbigel RT, McPeck M. Factors determining pulmonary deposition of aerosolized pentamidine in patients with human immunodeficiency virus infection. Am Rev Respir Dis 1991;143(4 Pt 1):727–737.
36. Rau JL, Zhu Y. Reservoir design and dose availability with long-term metered dose inhaler corticosteroid use. J Aerosol Med 1998; 11(1):15–26.
37. McPeck M, Tandon R, Hughes K, Smaldone GC. Aerosol delivery during continuous nebulization. Chest 1997;111()5:1200–1205.
38. Barry PW, O'Callaghan C. Drug output from nebulizers is dependent on the method of measurement. Eur Respir J 1998;12(2):463–466.
39. O'Riordan TG, Weinstein MD, Mao Y. Bench testing of nebulizers: a comparison of three methods. J Aerosol Med 1999;12(2):59–66.
40. Avent ML, Gal P, Ransom JL, Brown YL, Hansen CJ, Ricketts WA, Soza F. Evaluating the delivery of nebulized and metered-dose inhalers in an in vitro infant ventilator lung model. Ann Pharmacother 1999;33(2):144–148.
41. O'Doherty MJ, Thomas SHL, Page CJ, Treacher DF, Nunan TO. Delivery of a nebulized aerosol to a lung model during mechanical ventilation: effect of ventilator settings and nebulizer type, position, and volume of fill. Am Rev Respir Dis 1992;146(2):383–388.
42. Fuchs HJ, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Ramsey BW, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyome Study Group. N Engl J Med 1994;331(10):637–642.
43. Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. N Engl J Med 1999;340(1):23–30.
44. Newman SP. Scintigraphic assessment of therapeutic aerosols (review). Crit Rev Ther Drug Carrier Syst 1993;10(1):65–109.
45. Gonda I. Scintigraphic techniques for measuring in vivo deposition. J Aerosol Med 1996;9 Suppl 1:S59–S67.
46. Chan HK. Use of single photon emission computed tomography in aerosol studies (review). J Aerosol Med 1993;6(1):23–36.
47. Phipps PR, Gonda I, Bailey DL, Borham P, Bautovich, G, Anderson SD. Comparisons of planar and tomographic gamma scintigraphy to measure the penetration index of inhaled aerosols. Am Rev Respir Dis 1989;139(6):1516–1523.
48. Perring S, Summers Q, Fleming JS, Nassim MA, Holgate ST. A new method of quantification of the pulmonary regional distribution of aerosols using combined CT and SPECT and its application to nedocromil sodium administered by metered dose inhaler. Br J Radiol 1994;67(793):46–53.
49. Zainudin BMZ, Biddiscombe M, Tolfree SEJ, Short M, Spiro SG. Comparison of bronchodilator responses and deposition patterns of salbutamol inhaled from a pressurised metered dose inhaler, as a dry powder, and as a nebulised solution. Thorax 1990;45(6):469–473.
50. Dolovich M. The relevance of aerosol particle size to clinical response. J Biopharm Sci 1992;3:139–145.
51. Hultquist C, Wollmer P, Eklundh G, Jonson B. Effect of inhaled terbutaline sulphate in relation to its deposition in the lungs. Pulm Pharmac 1992;5(2):127–132.
52. Newman SP, Weisz AWB, Talaee N, Clarke SW. Improvement of drug delivery with a breath actuated pressurised aerosol for patients with poor inhaler technique. Thorax 1991;46(10):712–716.
53. Simonds AK, Newman SP, Johnson MA, Talaee N, Lee CA, Clarke SW. Alveolar targeting of aerosol pentamidine: toward a rational delivery system. Am Rev Respir Dis 1990;141(1):827–829.
54. Smaldone GC, Dickinson G, Marcial E, Young E, Seymour J. Deposition of aerosolized pentamidine and failure of pneumocystis prophylaxis. Chest 1992;101(1):82–87.
55. Smaldone GC. Deposition patterns of nebulized drugs: is the pattern important? J Aerosol Med 1994;7(Suppl 1):S25–S32.
56. Wigley FM, Londono JH, Wood SH, Shipp JC, Waldman RH. Insulin across respiratory mucosae by aerosol delivery. Diabetes 1971;20(8):552–556.
57. Laube BL, Georgopoulos A, Adams GK 3rd. Preliminary study of the efficacy of insulin aerosol delivered by oral inhalation in diabetic patients. JAMA 1993;269(16):2106–2109.
58. Laube BL, Benedict GW, Dobs AS. Time to peak insulin level, relative bioavailability, and effect of site of deposition of nebulized insulin in patients with noninsulin-dependent diabetes mellitus. J Aerosol Med 1998;11(3):153–173.
59. Hochhaus G, Möllmann H. Pharmacokinetic/pharmacodynamic characteristics of the β-2-agonists terbutaline, salbutamol and fenoterol (review). Int J Clin Pharmacol Ther Toxicol 1992;30(9):342–362.
60. Newnham DM, Lipworth BJ. Nebuliser performance, pharmacokinetics, airways and systemic effects of salbutamol given via a novel nebuliser delivery system ("Ventstream"). Thorax 1994;49(8):762–770.
61. Newman SP, Clarke SW. Bronchodilator delivery from Gentlehaler, a new low-velocity pressurized aerosol inhaler. Chest 1993; 103(5):1442–1446.
62. Newnham DM, McDevitt DG, Lipworth BJ. Comparison of the extrapulmonary β2-adrenoceptor responses and pharmacokinetics of salbutamol given by standard metered dose-inhaler and modified actuator device. Br J Clin Pharmacol 1993;36:445–450.
63. Clark DJ, Gordon-Smith J, McPhate G, Clark G, Lipworth BJ. Lung bioavailability of generic and innovator salbutamol metered dose inhalers. Thorax 1996;51(3):325–326.
64. Lipworth BJ, Clark DJ. Early lung absorption profile of non-CFC salbutamol via small and large volume plastic spacer devices. Br J Clin Pharmacol 1998;46(1):45–48.
65. Lipworth BJ, Clark DJ. Lung delivery of salbutamol given by breath activated pressurized aerosol and dry powder inhaler devices. Pulm Pharmacol Ther 1997;10(4):211–214.
66. Lipworth BJ, Clark DJ. Effects of airway calibre on lung delivery of nebulised salbutamol. Thorax 1997;52(12):1036–1039.
67. Anderson PJ, Zhou X, Breen P, Gann L, Logsdon TW, Compadre CM, Hiller FC. Pharmacokinetics of (R,S)-albuterol after aerosol inhalation in healthy adult volunteers. J Pharm Sci 1998;87(7):841–844.
68. Borgström L, Derom E, Stahl E, Wahlin-Boll E, Pauwels R. The inhalation device influences lung deposition and bronchodilating effect of terbutaline. Am J Respir Crit Care Med 1996;153(5): 1636–1640.

69. Borgström L, Newman S, Weisz A, Morén F. Pulmonary deposition of inhaled terbutaline: comparison of scanning gamma camera and urinary excretion methods. J Pharm Sci 1992;81(8):753–755.
70. Hindle M, Chrystyn H. Determination of the relative bioavailability of salbutamol to the lung following inhalation. Br J Clin Pharmacol 1992;34(4):311–315.
71. Hindle M, Newton DA, Chrystyn H. Dry powder inhalers are bioequivalent to metered-dose inhalers: a study using a new urinary albuterol (salbutamol) assay technique. Chest 1995;107(3):629–633.
72. Hindle M, Chrystyn H. Relative bioavailabiliy of salbutamol to the lung following inhalation using metered dose inhalation methods and space devices. Thorax 1994;49(6):549–553.
73. Hindle M, Newton DAG, Chrystyn H. Investigations of an optimal inhaler technique with the use of urinary salbutamol excretion as a measure of relative bioavailability to the lung. Thorax 1993;48(6): 607–610.
74. Clark DJ, Tan KS, Lipworth BJ. Evaluation of plasma and urinary salbutamol levels in COPD. Eur J Clin Pharmacol 1996;51(1):91–93.
75. Clark DJ, Lipworth BJ. Dose-response of inhaled drugs in asthma: an update (review). Clin Pharmacokinet 1997;32(1):58–74.
76. Pedersen S, Steffensen G, Ohlsson SV. The influence of orally deposited budesonide on the systemic availability of budesonide after inhalation from a Turbuhaler. Br J Clin Pharmacol 1993;36(3): 211–214.
77. Seale JP, Harrison LI. Effect of changing the fine particle mass of inhaled beclomethasone dipropionate on intrapulmonary deposition and pharmacokinetics (review). Respir Med 1998;92 Suppl A:9–15.
78. Harrison LI, Colice GL, Donnell D, Soria I, Dockhorn R. Adrenal effects and pharmacokinetics of CFC-free beclomethasone dipropionate: a 14-day dose-response study. J Pharm Pharmacol 1999; 51(3):263–269.
79. Riegelman RK. Studying a study and testing a test. Boston: Little, Brown; 1981: 21–27.
80. Margolis ML. PFT principles and bronchodilator testing in clinical practice: a guide for primary care physicians. Compr Ther 1998; 24(9):441–445.
81. Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society. Am Rev Respir Dis 1991;144(5):1202–1218.
82. Dompeling E, van Schayck CP, Molema J, Akkermans R, Folgering H, van Grunsven PM, van Weel C. A comparison of six different ways of expressing the bronchodilating response in asthma and COPD; reproducibility and dependence of prebronchodilator FEV_1. Eur Respir J 1992;5(8):975–981.
83. Eliasson O, Degraff AC Jr. The use of criteria for reversibility and obstruction to define patient groups for bronchodilator trials. Am Rev Respir Dis 1985;132(4):858–864.
84. Tweeddale PM, Alexander F, McHardy GJR. Short term variability in FEV_1 and bronchodilator responsiveness in patients with obstructive ventilatory defects. Thorax 1987;42(7):487–490.
85. Guyatt GH, Townsend M, Nogradi S, Pugsley SO, Keller JL, Newhouse MT. Acute response to bronchodilator: an imperfect guide for bronchodilator therapy in chronic airflow limitation. Arch Intern Med 1988;148(9):1949–1952.
86. Cazzola M, Vinciguerra A, Di Perna F, Matera MG. Early reversibility to salbutamol does not always predict bronchodilation after salmeterol in stable chronic obstructive pulmonary disease. Respir Med 1998;92(8):1012–1016.
87. Smith HR, Irvin CG, Cherniack RM. The utility of spirometry in the diagnosis of reversible airways obstruction. Chest 1992;101(6): 1577–1581.
88. Pellegrino R, Rodarte JR, Brusasco V. Assessing the reversibility of airway obstruction. Chest 1998;114(6):1607–1612.
89. Newhouse MT, Dolovich MB, Kazin F. Dose-effect relationship of the β-agonists fenoterol and salbutamol in patients with asthma. Chest 1994;105(6):1738–1742.
90. Mellen A, Arvidsson P, Palmqvist M, Lotvall J. Equivalent bronchodilation with salbutamol given via pMDI or Turbuhaler. Am J Respir Crit Care Med 1999;159(5 Pt 1):1663–1665.
91. Haahtela T, Vidgren M, Nyberg A, Korhonen P, Laurikainen K, Silvasti M. A novel multiple dose powder inhaler: salbutamol powder and aerosol give equal bronchodilatation with equal doses. Ann Allergy 1994;72(2):178–180.
92. Gross NJ, Petty TL, Friedman M, Skorodin MS, Silvers GW, Donohue JF. Dose response to ipratropium as a nebulized solution in patients with chronic obstructive pulmonary disease: a three-center study. Am Rev Respir Dis 1989;139(5):1188–1191.
93. Mestitz H, Copland JM, McDonald CF. Comparison of outpatient nebulized vs metered dose inhaler terbutaline in chronic airflow obstruction. Chest 1989;96(6):1237–1240.
94. Chapman KR, Friberg K, Balter MS, Hyland RH, Alexander M, Abboud RT, et al. Albuterol via Turbuhaler versus albuterol via pressurized metered-dose inhaler in asthma. Ann Allergy Asthma Immunol 1997;78(1):59–63.
95. Hansen EF, Phanareth K, Laursen LC, Kok-Jensen A, Dirksen A. Reversible and irreversible airflow obstruction as predictor of overall mortality in asthma and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159(4 Pt 1):1267–1271.
96. Turner MO, Patel A, Ginsburg S, FitzGerald JM. Bronchodilator delivery in acute airflow obstruction: a meta-analysis. Arch Intern Med 1997;157(15):1736–1744.
97. National Asthma Education and Prevention Program. Guidelines for the diagnosis and management of asthma. Expert Panel Report 2. 1997: 31–32.
98. Sly PD, Cahill P, Willet K, Burton P. Accuracy of mini peak flow meters in indicating changes in lung function in children with asthma. BMJ 1994;308(6928):572–574.
99. Reddel HK, Ware SI, Salome CM, Marks GB, Jenkins CR, Woolcock AJ. Standardization of ambulatory peak flow monitoring: the importance of recent β2-agonist inhalation. Eur Respir J 1998; 12(2):309–314.
100. Brand PLP, Duiverman EJ, Waalkens HJ, van Essen-Zandvliet EEM, Kerrebijn KF. Peak flow variation in childhood asthma: correlation with symptoms, airways obstruction, and hyperresponsiveness during long-term treatment with inhaled corticosteroids. Dutch CNSLD Study Group. Thorax 1999;54(2):103–107.
101. Tattersfield AE, Postma DS, Barnes PJ, Svensson K, Bauer CA, O'Byrne PM, et al. Exacerbations of asthma: a descriptive study of 425 severe exacerbations. The FACET International Study Group. Am J Respir Care Med 1999;160(2):594–599.
102. Verberne AAPH, Fuller R. An overview of nine clinical trials of salmeterol in an asthmatic population. Respir Med 1998;92(5):777–782.
103. Cockcroft DW, Swystun VA. Effect of single doses of S-salbutamol, R-salbutamol, racemic salbutamol, and placebo on the airway response to methacholine. Thorax 1997;52(10):845–848.
104. Juniper EF, Kline PA, Vanzieleghem MA, Ramsdale EH, O'Byrne PM, Hargreave FE. Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthmatics. Am Rev Respir Dis 1990;142(4):832–836.
105. Blake KV, Hoppe M, Harman E, Hendeles L. Relative amount of albuterol delivered to lung receptors from a metered-dose inhaler and nebulizer solution: bioassay by histamine bronchoprovocation. Chest 1992;101(2):309–315.
106. Douma WR, de Gooijer A, Rijcken B, Schouten JP, Koëter GH, Weiss ST, Postma DS. Lack of correlation between bronchocon-

strictor response and bronchodilator response in a population-based study. Eur Respir J 1997;10(12):2772–2777.
107. Sont JK, Willems LNA, Bel EH, van Krieken HJM, Vandenbroucke JP, Sterk P. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL Study Group. Am J Respir Crit Care Med 1999;159(4 Pt 1):1043–1051.
108. Haley KJ, Drazen JM. Inflammation and airway function in asthma: what you see is not necessarily what you get (review). Am J Respir Crit Care Med 1998;157(1):1–3.
109. Crimi E, Spanevello A, Neri M, Ind PW, Rossi GA, Brusasco V. Dissociation between airway inflammation and airway hyperresponsiveness in allergic asthma. Am J Respir Crit Care Med 1998; 157(1):4–9.
110. Bentley AM, Menz G, Storz C, Robinson DS, Bradley B, Jeffery PK, Durham SR, Kay AB. Identification of T lymphocytes, macrophages, and activated eosinophils in the bronchial mucosa in intrinsic asthma: relationship to symptoms and bronchial responsiveness. Am Rev Respir Dis 1992;146(2):500–506.
111. Kirby JG, Hargreave FE, Gleich GJ, O'Byrne PM. Bronchoalveolar cell profiles of asthmatic and nonasthmatic subjects. Am Rev Respir Dis 1987;136(2):379–383.
112. Jatakanon A, Kharitonov S, Lim S, Barnes PJ. Effect of differing doses of inhaled budesonide on markers of airway inflammation in patients with mild asthma. Thorax 1999;54(2):108–114.
113. Lim S, Jatakanon A, John M, Gilbey T, O'Connor BJ, Chung KF, Barnes PJ. Effect of inhaled budesonide on lung function and airway inflammation: assessment by various inflammatory markers in mild asthma. Am J Respir Crit Care Med 1999;159(1):22–30.
114. Cates CJ. Comparison of holding chambers and nebulisers for beta-agonists in acute asthma. The Cochrane Database of Systematic Reviews. The Cochrane Collaboration; Issue 3. Oxford: Update Software; 1996.
115. Carmichael J, Duncan D, Crompton GK. Beclomethasone dipropionate dry-powder inhalation compared with conventional aerosol in chronic asthma. Br Med J 1978;2(6138):657–658.
116. Bronsky E, Bucholtz GA, Busse WW, Chervinsky P, Condemi J, Ghafouri MA, et al. Comparison of inhaled albuterol powder and aerosol in asthma. J Allergy Clin Immunol 1987;79(5):741–747.
117. Agertoft L, Pedersen S. A randomized, double-blind dose reduction study to compare the minimal effective dose of budesonide Turbuhaler and fluticasone propionate Diskhaler. J Allergy Clin Immunol 1997;99(6 Pt 1):773–780.
118. Borg GAV. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14(5):377–381.
119. Wolkove N, Dajczman E, Colacone A, Kreisman H. The relationship between pulmonary function and dyspnea in obstructive lung disease. Chest 1989;96(6):1247–1251.
120. Moy ML, Lantin ML, Harver A, Schwartzstein RM. Language of dyspnea in assessment of patients with acute asthma treated with nebulized albuterol. Am J Respir Crit Care Med 1998;158(3):749–753.
121. Apter AJ, Affleck G, Reisine ST, Tennen HA, Barrows E, Wells M, et al. Perception of airway obstruction in asthma: sequential daily analyses of symptoms, peak expiratory flow rate, and mood. J Allergy Clin Immunol 1997;99(5):605–612.
122. Brand PL, Rijcken B, Schouten JP, Koëter, Weiss ST, Postma DS. Perception of airway obstruction in a random population sample: relationship to airway hyperresponsiveness in the absence of respiratory symptoms. Am Rev Respir Dis 1992;146(2):396–401.
123. O'Donnell DE, Lam M, Webb KA. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;160(2):542–549.
124. Jones PW. Issues concerning health-related quality of life in COPD (review). Chest 1995;107(5 Suppl):187S–193S.
125. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. Thorax 1987;42 (10):773–778.
126. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St George's Respiratory Questionnaire. Am Rev Respir Dis 1992; 145(6):1321–1327.
127. Hyland ME, Finnis S, Irvine SH. A scale for assessing quality of life in adult asthma sufferers. J Psychosom Res 1991;35(1):99–110.
128. Juniper EF, Johnston PR, Borkhoff CM, Guyatt GH, Boulet LP, Haukioja A. Quality of life in asthma clinical trials: comparison of salmeterol and salbutamol. Am J Respir Crit Care Med 1995;151(1):66–70.
129. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a sytematic review and meta-analysis. Arch Intern Med 1999;159(9):941–955.
130. Clark DJ, Grove A, Cargill RI, Lipworth BJ. Comparative adrenal suppression with inhaled budesonide and fluticasone proprionate in adult asthmatic patients. Thorax 1996;51(3):262–266.

Assessing Costs of Aerosol Therapy

Carlos A Camargo Jr MD DrPH and Patrick A Kenney

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[Respir Care 2000;45(6):756–763] *Key words: cost, assessment, aerosol, metered-dose inhaler, nebulizer.*

Introduction

Aerosol therapy (AT) is one of the most common respiratory treatments in the United States.[1] AT encompasses a wide array of medications that are delivered by an assortment of methods. Although AT is a broad and multifaceted term, the majority of AT is used to treat one condition: asthma.[2] Asthma affects approximately 15 million Americans,[3] and in recent years the prevalence of asthma has been increasing.[4] Most of these asthmatic patients suffer, on occasion, from exacerbations that require urgent AT. For example, there were nearly 2 million asthma-related emergency department (ED) visits in 1997,[5] and approximately 20–30% of ED visits result in admission.[4]

The increasingly large asthma burden underscores the importance of economically responsible therapy. According to the National Heart, Lung and Blood Institute, asthma cost an estimated $11 billion in 1998.[6] Because of this large cost, and since AT is the cornerstone of asthma treatment,[7–9] the costs of AT for asthma merit evaluation. This article examines a prominent issue in the field: comparison of β agonist delivery via nebulizer versus via pressurized metered-dose inhaler with spacer (MDI/spacer). This article introduces methods of critical evaluation through examination of selected analyses. It is not an exhaustive literature review. First, the article briefly introduces basic economic concepts. Familiarity with these terms is necessary for critical assessment of economic analyses. The selected literature reviewed compares outcomes of β agonist delivery via nebulizer and via MDI/spacer. Next we evaluate selected economic analyses of nebulizer and MDI/spacer treatment, and finally we present original data to demonstrate the great economic potential that remains for replacing nebulizers with MDI/spacers.

Basic Economic Concepts

Although this is a brief and highly simplified introduction to a complex field, familiarity with basic economic

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concepts will help us decipher the conclusions of existing cost analyses. To begin, a cost is a measurement of resource consumption.[10] It is an expenditure or a loss. When conducting any cost study, one must identify those who bear the burden of the costs. Costs can be valued from numerous perspectives, including those of society as a whole, the caregiver or hospital, the patient, or the employers of patients.

There are several categories of costs with which we will be concerned: direct or indirect, and fixed or variable. Direct costs are equivalent to the outlay or amount paid for an object or service. Direct costs are expenditures or transactions for goods or services, such as medications or labor.[10] On the other hand, indirect costs are losses and other expenses that are not immediately incurred. For example, lost economic productivity due to morbidity is an indirect cost of a disease. For a patient, time spent in an ED as opposed to in the workplace produces indirect costs.

Most costs can be characterized as either fixed or variable. A fixed cost does not vary with volume in the short term.[11,12] For example, when an additional patient visits an ED, the fixed salary costs of the ED are not affected. On the other hand, variable costs are volume-dependent in the short term.[11] An ED's variable costs for items such as medications or gloves are directly influenced by patient volume.

Limitations of Cost-Effectiveness Analysis

A useful method of evaluating two different interventions (eg, nebulizer vs MDI/spacer) is to assess their cost-effectiveness. Cost-effectiveness analysis compares the outcomes of different interventions in relation to their costs. An intervention is cost-effective only in relation to another course of action.[13] Though it is a useful tool, the conclusions of a cost-effectiveness study are not always clear cut. For instance, it is possible that a cost analysis would determine that an intervention results in slightly improved outcomes at increased expense. Cost-effectiveness analysis does not guarantee simple judgments.

Although both nebulizers and MDI/spacers perform the same task (ie, medication delivery), comparing the outcomes of the two methods is not easy. In general, patient outcomes in AT are proportionally related to the quantity of medication deposited in the patient's lungs.[14] Patient outcomes can vary widely because of many factors that affect medication deposition.[8] It is difficult to accurately predict how outcomes will vary across different delivery methods or even among patients who use the same delivery method.

In addition, the costs of delivery methods are not constant. Equipment, medication, and labor costs vary between different treatment locations. For example, in a high-volume ED, fixed costs may be spread out sufficiently among patients that a method is economically sound in that ED. By contrast, the same method might not be a sound choice for a low-volume ED or general outpatient clinic. In another example, it may make sense for a large hospital to employ a respiratory therapist (RT) to deliver treatments. In a small hospital, it may be more prudent to transfer these responsibilities to other medical staff.

Since neither the outcomes nor costs of the two delivery methods in question are consistent or easily generalized, cost-effectiveness analysis is difficult to perform and to interpret. Economic analyses operate on important assumptions and rely heavily on simplification. For these reasons, it is not entirely accurate to perform an analysis that will, in the end, broadly declare one delivery method (ie, nebulizer or MDI/spacer) more cost-effective than another.

Nebulizers and MDI/Spacers Produce Equivalent Outcomes

Despite the great potential for variation in individual patient outcomes, AT reviews have concluded that outcomes are broadly equivalent between nebulizers and MDI/spacers.[9,15] In 1997 Turner et al[9] published a review of 12 studies that compared bronchodilator delivery via nebulizer to via MDI/spacer.[16–27] The articles reviewed were all randomized, clinical trials of adult patients with acute asthma or chronic obstructive pulmonary disease in the ED or hospital, and measured initial patient outcomes in terms of forced expiratory volume in the first second or peak expiratory flow. Turner et al concluded that there was no difference in initial outcomes between patients who received bronchodilator via nebulizer and those who received it via MDI/spacer. (Spacers were used in all but two of the studies.) Since initial measures of bronchoconstriction demonstrated equivalence of the two methods, the authors maintained that other outcomes would likely be equivalent as well. It is important to note that patients who were unable to properly use the MDI/spacer because of the severity of their illness, lack of coordination, or inability to hold breath were excluded from some of the reviewed studies, and this might have introduced an important selection bias.

In a Cochrane Library meta-analysis that was last updated in February 1998, Cates compared the clinical outcomes of acute asthma patients who received β agonists via nebulizer versus MDI/spacer.[15] (The Cochrane Library is accessible at http://www.update-software.com/cochrane.htm). Cates reviewed 13 randomized controlled trials in both adult and pediatric patients[19,22,24,25,28–36] and concluded that the outcomes of nebulizer patients were equivalent to MDI/spacer patients. (Four of the 13 reviewed articles were also included in the review by Turner et al[9]). The 13 trials measured clinical outcomes in a variety of ways, including hospital admission, length of stay

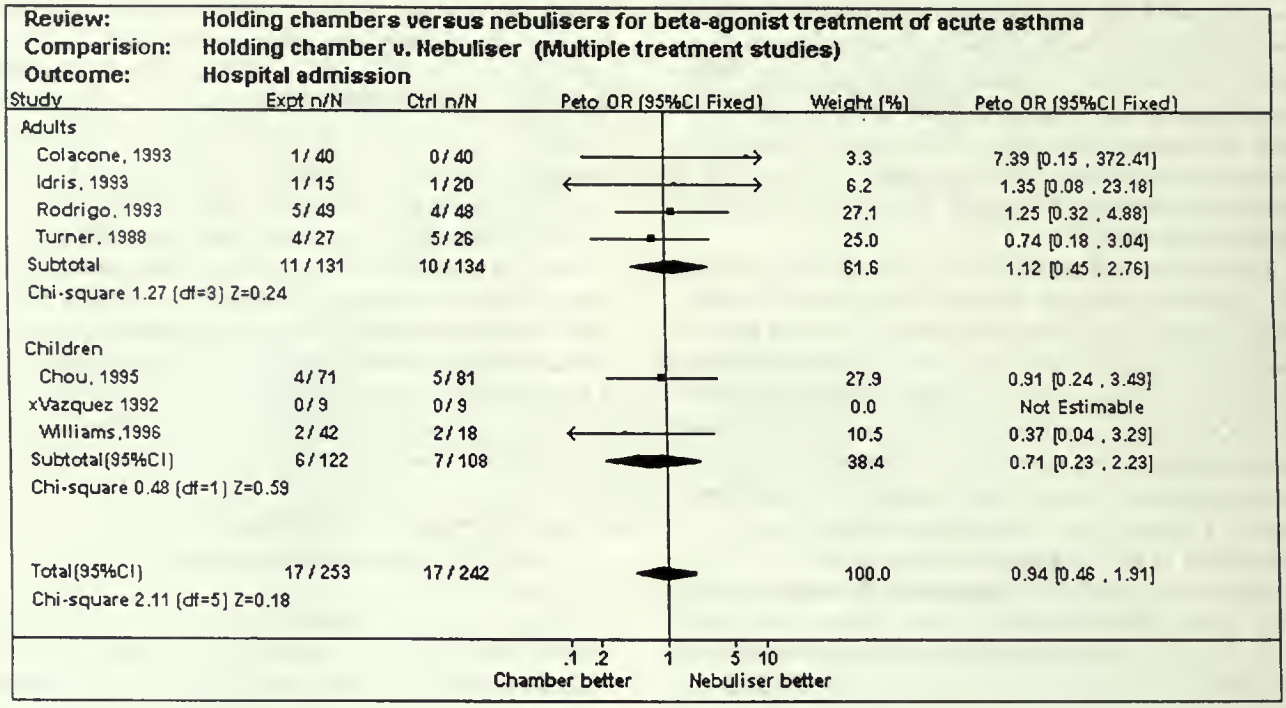
Review: Holding chambers versus nebulisers for beta-agonist treatment of acute asthma
Comparision: Holding chamber v. Nebuliser (Multiple treatment studies)
Outcome: Hospital admission
Study
Expt n/N
Ctrl n/N
Peto OR (95%CI Fixed)
Weight (%)
Peto OR (95%CI Fixed)
Adults
Colacone, 1993 1/40 0/40 3.3 7.39 [0.15 , 372.41]
Idris, 1993 1/15 1/20 6.2 1.35 [0.08 , 23.18]
Rodrigo, 1993 5/49 4/48 27.1 1.25 [0.32 , 4.88]
Turner, 1988 4/27 5/26 25.0 0.74 [0.18 , 3.04]
Subtotal 11/131 10/134 61.6 1.12 [0.45 , 2.76]
Chi-square 1.27 (df=3) Z=0.24
Children
Chou, 1995 4/71 5/81 27.9 0.91 [0.24 , 3.49]
xVazquez 1992 0/9 0/9 0.0 Not Estimable
Williams,1996 2/42 2/18 10.5 0.37 [0.04 , 3.29]
Subtotal(95%CI) 6/122 7/108 38.4 0.71 [0.23 , 2.23]
Chi-square 0.48 (df=1) Z=0.59
Total(95%CI) 17/253 17/242 100.0 0.94 [0.46 , 1.91]
Chi-square 2.11 (df=5) Z=0.18
.1 .2 1 5 10
Chamber better
Nebuliser better

Fig. 1. Hospital admission did not vary between metered-dose inhaler with spacer and nebulizer patients in Cates' Cochrane Library Review. (From Reference 15, with permission.)

in the ED, respiratory and pulse rates, blood gases, and lung function. According to Cates, none of these outcomes was worse in patients with acute asthma who used MDI/spacers rather than nebulizers (Fig. 1).

Cates pointed out several limitations to the studies he reviewed. It is not known whether the results are applicable to inpatient or community care, since 12 of the 13 studies were confined to the ED. Only three of the studies analyzed lung function outcomes in patients whose forced expiratory volume in the first second was $< 30\%$ of predicted. These 3 studies concluded that even in severe exacerbations the two delivery methods produced similar outcomes.[15] Since patients with the most severe life-threatening exacerbations were excluded from the majority of the 13 studies, the review's conclusion cannot necessarily be applied to these patients. Cates also points out that there is little information on the number of patients who were excluded from the 13 studies. To what degree the studies' results are applicable to all acute asthma patients is therefore unknown.

Cost Analysis of the Two Delivery Methods

Despite these methodologic concerns, both reviews conclude that nebulizers and MDI/spacers can produce equivalent outcomes in bronchodilator delivery. Generally speaking, the less costly of the two will therefore be the most cost-effective. Studies have found that AT via nebulizer is more costly than via MDI/spacer, and several analyses have suggested that hospitals could reduce costs by switching to MDI/spacers.[16,37–40] Of those analyses reviewed, the cost study that estimates the largest savings is based on a problematic analysis.[16] Detailed examination of this study provides an interesting introduction to cost analysis, helps identify potential areas of improvement, and demonstrates the importance of critically evaluating cost analyses. Subsequent studies are based on improved methodology and predict more modest savings.

An Important Preliminary Effort

In 1987, Jasper et al published a study that compared "therapist-administered" nebulization to "self-administered" MDI/spacer in an inpatient setting.[16] The authors randomized 34 nonintensive care unit (non-ICU) patients with a diagnosis of obstructive lung disease into 2 groups. The randomization was stratified by diagnosis—either asthma or chronic obstructive pulmonary disease. One group received inhaled treatment via nebulizer and the other received inhaled treatment via MDI/spacer. As one would expect, the study concluded that there were no significant differences in patient outcomes between the 2 groups. More importantly, Jasper et al also found that nebulizer treatment was more costly than MDI/spacer. First, the authors calculated 1985 costs while assuming that all treatments were administered via nebulizer. Then, they

calculated 1985 costs while assuming that all treatments were given via MDI/spacer. According to their analysis, if all nebulized treatments were replaced with MDI/spacer in their 900-bed teaching hospital, the hospital would save over $250,000 a year.

This savings estimate is striking, though it probably is overly optimistic. To begin, the investigators excluded patients with "physical or mental inability to assemble the MDI."[16] Clearly, a patient who is physically or mentally unable to operate the MDI/spacer would not have been able to achieve the same outcome with an MDI/spacer as with a nebulizer. Thus, selection bias may have influenced the report's outcome findings. Though the authors *excluded* these patients from the outcomes analysis, it appears that these patients were *included* in the savings estimate. Cost calculations were based on a complete AT audit.[16] The $250,000 potential savings estimate is dependent on *full* conversion from nebulizer to MDI/spacer. The hospital could achieve the predicted savings only if patients whom the investigators originally deemed inappropriate candidates for MDI/spacer treatment were converted from nebulizer to MDI/spacer.

According to an article by Turner et al,[40] the authors also overestimated the labor necessary to administer a nebulizer treatment. Jasper et al[16] estimated that 20 minutes of labor by an RT is needed to deliver each nebulizer treatment. In contrast, time and motion studies by Turner et al found that only 4 minutes of labor is necessary to deliver a nebulizer treatment.[40] Adjusting the treatment costs accordingly would reduce the hospital's net savings from $250,000 to $30,000. However, according to other analyses, a labor estimate between 4 minutes and 20 minutes is likely to be the most accurate.[38,39] Reducing the Jasper et al nebulizer labor estimate even by half would deflate the savings estimate to $113,800.

In addition, the authors treated the fixed salary of the therapist as a variable cost. By reporting the cost of RT labor in a variable, 20-minute unit, the authors imply that the hospital's RT cost varies with nebulizer treatment volume in the short term. This is not the case. For instance, if an RT administers only one 20-minute nebulizer treatment on a quiet day, the model promoted by Jasper et al[16] would only account for $5.94 in labor costs. Yet, since the RT is paid a fixed annual salary, the hospital's labor cost for that day is greater than $5.94. As Roberts et al point out, being able to reap savings associated with fixed costs is a vital component of cost analysis.[11] Introduction of alternative interventions may actually increase a hospital's costs unless fixed costs such as salaries are eliminated.[11] The hospital only would reap labor savings if the reduction in nebulizer treatments is large and lasting. In this case, the hospital would need to terminate 7 RTs to achieve the savings predicted by Jasper et al[16] (Table 1).

Table 1. Accessing Savings in Fixed Labor Costs in Cost-Analysis

20-minutes RT labor/nebulizer treatment × 47,038 nebulizer treatments/year = 15,680 hours RT labor/year.
1 RT works 40 hours/week × 49 weeks/year = 1,960 hours/year/therapist.
15,680 hours of treatment/year ÷ 1,960 hours/year/therapist = 8 therapists needed to deliver nebulizer treatments.

One MDI instructional session/admitted patient × 3,680 admissions/year = 3,680 instructional sessions/year.
$5.94 per instructional session = 20 minutes of RT labor.
3,680 instructional sessions/year × 20 minutes RT labor/instructional session = 1,230 hours RT labor/year.
1,230 hours RT labor needed per year ÷ 1,960 hours/year/therapist ≈ 1 therapist needed to give MDI instructional sessions.

If nebulizer treatments are replaced by self-administered MDI treatments, only 1 of the 8 RTs is still needed for this purpose.
To achieve $250,000 savings prediction of Jasper et al, 7 of the 8 RTs would need to be terminated.

RT = respiratory therapist. MDI = metered-dose inhaler.
(Adapted from Reference 16).

It is noteworthy that even if the hospital terminated 7 RTs, the associated savings would not be as great as the savings predicted by Jasper et al. By recording labor as a variable cost, Jasper et al imply that the hospital paid only for the cost of the 1,230 hours during which instructional sessions would have been given. The hospital may have to pay the remaining RT $13,000 for 730 hours (1,960 paid hours per year: 1,230 hours worked) during which the RT would perform no instructional sessions. Misclassification of labor as a variable cost may overestimate the savings associated with replacement of nebulizers with MDI/spacers.

Jasper et al[16] claimed that "hundreds of millions of dollars" could be saved by national implementation of their plan. Yet, the analysis by Jasper et al is problematic and does not adequately demonstrate that their predicted savings could truly be achieved. Their $250,000 savings estimate is based on overestimation of the level to which substitution can be achieved on inflated nebulizer labor costs, on unrecorded MDI/spacer labor costs, and finally, on misclassification of fixed costs as variable. The authors' implicit recommendation to fire RTs en masse is not justified by their analysis. The study by Jasper et al is a detailed analysis, but methodological problems limit its success. However, subsequent analyses support the authors' conclusion that nebulizer treatment is more costly than MDI/spacer.

Economic analysis is a difficult undertaking. Several additional articles briefly mention nebulizer versus MDI/spacer cost considerations,[17,22,37,41,42] but add little to the detailed article by Jasper et al.[16] A 1999 article by Dewar

et al exemplifies the many obstacles that investigators may encounter and the need for detailed analysis.[37] Dewar et al compared the costs of medication delivery via nebulizer and via MDI/spacer in two United Kingdom hospitals. The investigators studied children over the age of three who were admitted to one of the two hospitals for acute asthma. When calculating the cost of treatment, the authors included equipment and hardware costs, but failed to account for labor. Labor costs were rightly a key component of the study by Jasper et al.[16] Moreover, Dewar et al provided no detailed breakdown of the costs included in their analysis. They concluded that nebulizer treatment was 4 times as costly as MDI/spacer treatment. Thus, the authors deemed MDI/spacer treatment a "cost effective option for asthma management"[37] based on an analysis that ignored the most important component of medication delivery costs, and without providing any detail about the costs that were included.

Improved Analyses and Moderated Savings

In 1992, Bowton et al provided a more detailed and well-structured cost analysis.[39] Over a period of 4 months at their 700-bed university hospital, orders for nebulized β agonist therapy were considered for MDI/spacer substitution. Nebulizer therapy was not replaced if the ordering physician refused substitution, if the patient was unable to comply with instructions, or if the RT determined that the patient was unable to properly use the MDI/spacer. The investigators based labor usage on time-management studies. They estimated that each nebulizer treatment for non-ICU patients required 12 minutes of work by an RT. Initial setup and instruction of non-ICU, spontaneously-breathing patients for MDI/spacer treatment required only 9 minutes. Each additional MDI/spacer treatment required only 5 minutes of RT labor. Thus, less RT labor was consumed when nebulizer treatments were replaced with MDI/spacer treatments (Fig. 2).

Like Jasper et al,[16] Bowton et al predicted that conversion to MDI/spacer would produce savings. But, unlike Jasper et al, who assumed 100% conversion, Bowton et al based their savings estimate on the true extent to which they were able to achieve conversion to MDI/spacer. Before the intervention, no treatments were given via MDI/spacer. After 1 month, 54% of non-ICU patients received all treatments via MDI/spacer. After 4 months of consistent attempts at conversion, 62% of all AT was delivered via MDI/spacer in non-ICU patients. In ICUs, 49% of treatments were delivered via MDI/spacer after 1 month, and 79% after 4 months. The average cost per AT treatment declined from $3.60 to $2.47. The hospital's monthly AT cost declined from $27,600 to $20,600. The authors predicted that up to $83,000 could be saved per year if the hospital continued to deliver 60% of AT via MDI/spacer.

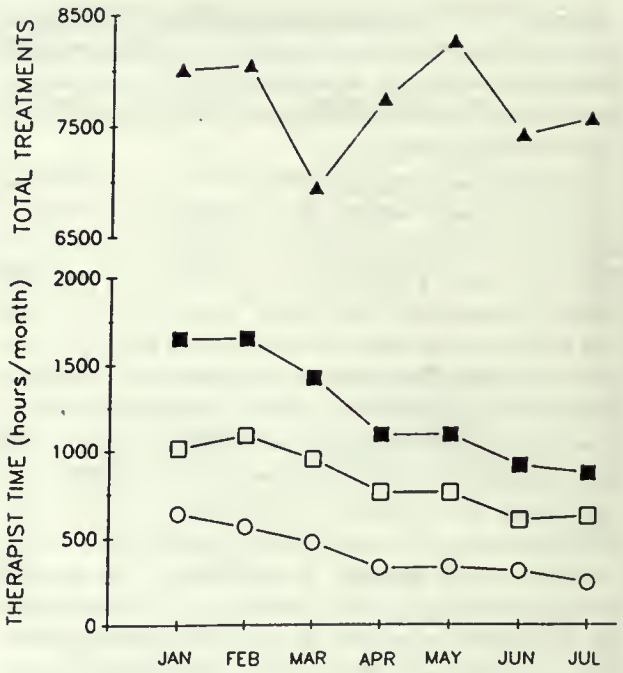

Fig. 2. Therapist time and aerosol treatments per month in a cost analysis by Bowton et al. The upper portion of the figure shows the number of aerosol treatments in the hospital per month. The lower portion of the figure shows the hours of therapist labor needed to administer these treatments in general care areas (open circles), in the ICU (open squares), and in the hospital as a whole (closed squares). The hours of therapist labor needed to deliver aerosol treatments is lower after onset, in April, of an initiative to replace nebulizers with metered-dose inhalers with spacers. There was not a concurrent decline in the total number of treatments. (From Reference 39, with permission.)

Like Jasper et al, the authors included costs of all relevant medication and equipment. In addition, Bowton et al accounted for labor costs in a consistent, logical manner. Though they recorded labor costs in the same potentially problematic "per treatment" fashion as Jasper et al, they addressed the shortcomings of this approach. They noted that when nebulizer therapy is replaced with MDI/spacer, RT time must be redirected productively. If not, "a reduction in the work force commensurate with the reduction in the work load must take place" for the hospital to save money.[39] Simply converting patients to MDI/spacer therapy does not engender savings; savings must be actively pursued.

To their credit, the investigators examined the effect of conversion to MDI/spacer on RT productivity. Bowton et al discovered that RTs used their newfound time to deliver other therapy for which the hospital was able to charge patients. The hospital's AT cost was reduced by partial conversion to MDI/spacer treatment, and the conserved labor resources were then redirected toward other, chargeable therapy. The authors conceded that the $83,000 in savings are "potential," and that actual savings depend on

RT productivity. They argue that although savings may vary from institution to institution, a reduction in costs and improved usage of RTs is likely.[39]

A 1991 study by Orens et al converted a smaller percentage of patients from nebulizer treatment to MDI/spacer but still demonstrated cost savings.[38] As in other studies, the investigators examined the effect of an effort to increase MDI/spacer use on costs. In the first year of the program, only 5% of treatments were administered via MDI/spacer. In the following year, 18% of all bronchodilator treatments were administered via MDI/spacer, and, in the investigators' opinion, higher MDI/spacer utilization rates are possible. This judgment is consistent with the findings of Bowton et al.[39]

Orens et al[38] also tallied all relevant equipment, medication, and labor costs. Labor usage was tallied by a real-time hand-held computer system to which the authors credited improved labor estimates. The authors concluded that conversion of 18% of the 70,000 total aerosol treatments to MDI/spacer saved the Cleveland Clinic Foundation $26,510 in 1989. Once again, the main source of savings was reduced labor costs. As shown by examination of the article by Jasper et al,[16] reductions in the workforce are necessary to access these savings unless, as Bowton et al[39] discovered, labor savings can be reinvested in the institution.

In a 1996 study, Turner et al provided a cost analysis of delivery methods in a Canadian teaching hospital.[40] Over a 6-week period, the investigators audited AT of 95 patients, of which 71% received treatment via nebulizer, 6% received treatment via MDI, and 23% received treatment via both methods. As in previous studies, Turner et al recorded costs for equipment, medication, and labor. Motion studies were used to estimate labor times. However, as discussed earlier, Turner et al's 4-minute labor estimate for nebulizer therapy is substantially shorter than other estimates. In accordance with earlier findings, the authors concluded that self-administration of MDI treatments (without use of a spacer) is the least costly delivery method. According to Turner et al, if more than 4 minutes of labor is needed to deliver a nebulizer treatment, even MDI treatments that are not self-administered are a less costly alternative. Unlike other studies, the conclusions of this analysis were tested by sensitivity analysis.

On the whole, Bowton et al,[39] Orens et al,[38] and Turner et al[40] produced useful studies that addressed many of the shortcomings of the study by Jasper et al.[16] However, none of these studies included all relevant direct costs to the hospitals. For example, the studies did not address the startup costs of MDI/spacer conversion programs. Startup costs, such as the cost of educating RTs and nurses in proper MDI/spacer actuation, increase the costs associated with replacing nebulizers with MDI/spacers. As a result, potential savings will not be as high as predicted. Startup costs are a necessary component of a cost analysis and they warrant investigation.

Moving Toward a Better Model

By examining these studies, we may move toward a better model of delivery method cost analysis. Economic studies must include all relevant costs, including startup, medication, equipment, and labor. Accounting for labor usage and cost has been shown to be a problematic and difficult task. Whereas Jasper et al calculated nebulizer labor costs based on a simple estimate, Bowton et al, Orens et al, and Turner et al observed actual labor usage.[16,38–40] Turner et al arrived at a much smaller labor estimate. The disparity of nebulizer labor estimates suggests that further research would be beneficial. In addition, Orens et al, Bowton et al, and Turner et al assessed labor costs for all MDI/spacer treatments, not just an initial MDI/spacer instructional session and treatment.

Although each study recorded labor in a variable, "per treatment" unit, labor savings are not as easily accessible as equipment or medication savings. Unlike individually packaged vials of medicine, labor is a cost that does not vary directly with volume in the short term. Determining the labor cost per minute and multiplying that figure by the number of minutes expended on a therapy ignores that a hospital's labor payments are fixed in the short term. Costs should be clearly identified as variable or fixed, and the consequences of this designation must be stated. Finally, a savings estimate must be based on the true number of aerosol treatments that can be given via MDI/spacer. Jasper et al[16] used an idealized number. Bowton et al[39] and Orens et al[38] more realistically accepted that nebulizers will remain the primary delivery method for some patients.

The studies in question calculated only direct costs from hospitals' perspective. Each of the studies ignored indirect costs and costs to nonhospital entities. Although calculating direct costs to the hospital is not an inherently problematic practice, it limits the conclusions that a study can reach. In an effort to be more complete, direct costs from perspectives other than that of the hospital could be included. Indirect costs, such as those associated with adverse effects, the environmental impact of MDI chlorofluorocarbons, or the potential for nebulizer cross-contamination could also be recorded.

A Future Consideration

The reviewed studies all concluded that *the majority* of savings are derived from the less labor-intensive nature of MDI/spacer treatment. In part, this conclusion is based on the relatively low cost of albuterol. In general, 2–10% of the expended dose is deposited in the lungs in nebulizer treatment.[43] On the other hand, an MDI/spacer deposits

10–25% of the expended dose in the lungs.[8] MDI/spacers will become more attractive with increasing medication costs, since they deposit more of the expended dose in the lungs. In other words, if the cost of albuterol were to increase, or if a more expensive medicine replaced albuterol, the impetus to increase MDI/spacer use would be even greater. Cost-effectiveness studies have thereupon identified a basic goal: hospitals should seek adoption of a delivery method that is not labor intensive, and that properly deposits a high percentage of expended medication.

Conversion to MDI/Spacer Therapy: An Untapped Opportunity

Studies suggest that there is substantial benefit to increased MDI/spacer use. Although total conversion is not feasible, studies show that a percentage of patients can replace nebulizer with MDI/spacer.[38,39,41] An examination of original data from the Multicenter Airway Research Collaboration (MARC) demonstrates that large potential savings still exist.

We combined data from 4 prospective cohort studies performed during 1996 to 1998.[44] Using a standardized protocol, MARC investigators at 64 academic EDs in 21 of the United States and 4 Canadian provinces provided 24-hour-per-day coverage for a median of two weeks. The Institutional Review Board at each of the 64 hospitals approved the study. Inclusion criteria were physician diagnosis of acute asthma, age 18–54, and the ability to give informed consent. All patients were managed at the discretion of the treating physician. Repeat visits by individual subjects were excluded (n = 149), as were patients with lost medical records (n = 25). Of 2,496 eligible patients, 1,847 (74%) patients with acute asthma were enrolled.

Strikingly, MARC data suggest that only 5% (95% confidence interval 4–6%) of adults who present to an academic ED with acute asthma receive at least one β agonist treatment via MDI. Only 2% (95% confidence interval 2–3%) of patients receive β agonist via MDI alone. Of the 64 sites, only 23 EDs (36%, 95% confidence interval 24–49%) gave at least one β agonist treatment via MDI during the two-week enrollment period. Thus, in the academic ED setting, the potential savings of MDI/spacer therapy have yet to be realized.

Summary

The large economic burden of asthma accentuates the need for economically sound treatment. Numerous studies report that the outcomes produced by nebulizers are equivalent to the outcomes produced by MDI/spacers in selected patients. Studies show that MDI/spacer use will probably result in substantial cost savings to hospitals.[16,38–40] Although some patients will not be able to achieve the same outcomes with MDI/spacers as with nebulizers, Bowton et al and Orens et al showed that a large percentage of patients could be converted to the less costly MDI/spacer therapy without negative repercussions.[38,39]

Observation of current treatment practice indicates that hospitals have yet to capitalize on the economic benefits of replacing nebulizers with MDI/spacers. For example, original data from MARC indicate that only 5% of adults who present to an academic ED with acute asthma receive at least one β agonist treatment via MDI. Studies that improve upon existing cost analyses may convince hospitals of the untapped savings potential. Investigation of barriers to MDI/spacer conversion, along with a compilation of successful strategies for this conversion, would be helpful. Taken together, such research could lead to increased β agonist delivery via MDI/spacer and probable savings to the health care system.

REFERENCES

1. Giordano SP. Aerosol therapy: the hard questions (editorial). Respir Care 1991;36(9):914–915.
2. Svedmyr N. Clinical advantages of the aerosol route of drug administration. Respir Care 1991;36(9):922–930.
3. Data fact sheet: asthma statistics. National Heart, Lung, and Blood Institute web site. Available at http://www.nhlbi.nih.gov/health/prof/lung/asthma/asthstat.pdf. Accessed Aug 20, 1999.
4. Camargo CA Jr, Richardson LD. Epidemiology of asthma. In: Brenner BE, editor. Emergency asthma. New York: Marcel Dekker; 1999: 59–80.
5. Nourjah P. National hospital ambulatory medical care survey: 1997 emergency department summary. Advance data from vital and health statistics; No. 304. Hyattsville, MD: National Center for Health Statistics; 1999.
6. Morbidity & Mortality. 1998 chartbook on cardiovascular, lung and blood diseases. National Heart, Lung, and Blood Institute web site. Available at http://www.nhlbi.nih.gov/resources/docs/98chtbk.pdf. Accessed Aug 20, 1999.
7. Amirav I, Newhouse MT. Metered-dose inhaler accessory devices in acute asthma: efficacy and comparison with nebulizers: a literature review. Arch Pediatr Adolesc Med 1997;151(9):876–882.
8. Newman SP. Aerosol generators and delivery systems. Respir Care 1991;36(9):939–951.
9. Turner MO, Patel A, Ginsburg S, FitzGerald JM. Bronchodilator delivery in acute airflow obstruction: a meta-analysis. Arch Intern Med 1997;157(15):1736–1744.
10. Eisenberg JM. Clinical economics: a guide to the economic analysis of clinical practices (review). JAMA 1989;262(20):2879–2886.
11. Roberts RR, Frutos PW, Ciavarella GG, Gussow LM, Mensah EK, Kampe LM, et al. Distribution of variable vs fixed costs of hospital care. JAMA 1999;281(7):644–649.
12. Finkler SA. The distinction between cost and charges. Ann Intern Med 1982;96(1):102–109.
13. Doubilet P, Weinstein MC, McNeil BJ. Use and misuse of the term "cost effective" in medicine. N Engl J Med 1986;314(4):253–256.
14. Dolovich M. Inhalation technique and inhalation devices. In: Pauwels R, O'Byrne PM, editors. Beta2-agonists in asthma treatment. New York: Marcel Dekker; 1997: 229–251.

15. Cates CJ. Holding chambers versus nebulizers for beta agonist treatment of acute asthma (Cochrane Review). In: The Cochrane Library, Issue 3, 1999. Oxford: Update Software.
16. Jasper AC, Mohsenifar Z, Kahan S, Goldberg HS, Koerner SK. Cost-benefit comparison of aerosol bronchodilator delivery methods in hospitalized patients. Chest 1987;91(4):614–618.
17. Summer W, Elston R, Tharpe L, Nelson S, Haponik EF. Aerosol bronchodilator delivery methods: relative impact on pulmonary function and cost of respiratory care. Arch Intern Med 1989;149(3):618–623.
18. Cayton RM, Webber B, Paterson JW, Clark TJ. A comparison of salbutamol given by pressure-packed aerosol or nebulization via IPPB in acute asthma. Br J Dis Chest 1978;72(3):222–224.
19. Colacone A, Afilalo M, Wolkove N, Kreisman H. A comparison of albuterol administered by metered dose inhaler (and holding chamber) or wet nebulizer in acute asthma. Chest 1993;104(3):835–841.
20. Berenberg MJ, Baigelman W, Cupples LA, Pearce L. Comparison of metered-dose inhaler attached to an Aerochamber with an updraft nebulizer for the administration of metaproterenol in hospitalized patients. J Asthma 1985;22(2):87–92.
21. Berry RB, Shinto RA, Wong FH, Despars JA, Light RW. Nebulizer vs spacer for bronchodilator delivery in patients hospitalized for acute exacerbations of COPD. Chest 1989;96(6):1241–1246.
22. Idris AH, McDermott MF, Raucci JC, Morrabel A, McGorray S, Hendeles L. Emergency department treatment of severe asthma: metered-dose inhaler plus holding chamber is equivalent in effectiveness to nebulizer. Chest 1993;103(3):665–672.
23. Maguire GP, Newman T, DeLorenzo LJ, Brown RB, Stone D. Comparison of a hand-held nebulizer with a metered dose inhaler-spacer combination in acute obstructive pulmonary disease. Chest 1991; 100(5):1300–1305.
24. Salzman GA, Steele MT, Pribble JP, Elenbaas RM, Pyszczynski DR. Aerosolized metaproterenol in the treatment of asthmatics with severe airflow obstruction: comparison of two delivery methods. Chest 1989;95(5):1017–10120.
25. Turner JR, Corkery KJ, Eckman D, Gelb AM, Lipavsky A, Sheppard D. Equivalence of continuous flow nebulizer and metered-dose inhaler with reservoir bag for treatment of acute airflow obstruction. Chest 1988;93(3):476–481.
26. Hodder RV, Calcutt LE, Leech JA: Metered dose inhaler with spacer is superior to wet nebulization for emergency room treatment of acute, severe asthma (abstract). Chest 1988; 94(suppl):52S.
27. Moss K, McDonald A, Ferrara L, Myles D, Brischetto M. Metered dose inhaler vs compressor driven nebulizer in the delivery of metaproterenol. Chest 1985;100:1300–1305.
28. Chou KJ, Cunningham SJ, Crain EF. Metered-dose inhalers with spacers vs nebulizers for pediatric asthma. Arch Pediatr Adolesc Med 1995;149(2):201–205.
29. Freelander M, Van Asperen PP. Nebuhaler versus nebuliser in children with acute asthma. Br Med J (Clin Res Ed) 1984;288(6434): 1873–1874.
30. Kerem E, Levison H, Schuh S, O'Brodovich H, Reisman J, Bentur L, Canny GJ. Efficacy of albuterol administered by nebulizer versus spacer device in children with acute asthma. J Pediatr 1993;123(2): 313–317.
31. Lin YZ, Hsieh KH. Metered dose inhaler and nebuliser in acute asthma. Arch Dis Child 1995;72(3):214–218.
32. Morrone N, Freire JA, Pereira CA, Ferreira AK. [Bronchodilation induced by fenoterol in asthmatic patients: comparison of jet nebulization and spacer device.] Rev Paul Med 1990;108(2):83–87. Article in Portugese.
33. Pendergast J, Hopkins J, Timms B, Van Asperen PP. Comparative efficacy of terbutaline administered by Nebuhaler and by nebulizer in young children with acute asthma. Med J Aust 1989;151(7):406–408.
34. Williams JR, Bothner JP, Swanton RD. Delivery of albuterol in a pediatric emergency department. Pediatr Emerg Care 1996;12(4): 263–267.
35. Rodrigo G, Rodrigo C. Comparison of salbutamol delivered by nebulizer or metered-dose inhaler with a pear-shaped spacer in acute asthma. Curr Ther Res - Clin Exp 1993;54:797–808.
36. Vazquez CC. [Comparison of treatment of acute asthma attacks in children with salbutamol dispensed by the Volumatic dispenser or by a nebulizer.] An Esp Pediatr 1992;36(5):359–62. Article in Spanish.
37. Dewar AL, Stewart A, Cogswell JJ, Connett GJ. A randomised controlled trial to assess the relative benefits of large volume spacers and nebulisers to treat acute asthma in hospital. Arch Dis Child 1999; 80(5):421–423.
38. Orens DK, Kester L, Fergus LC, Stoller JK. Cost impact of metered dose inhalers vs small volume nebulizers in hospitalized patients: the Cleveland Clinic experience. Respir Care 1991;36(10):1099–1104.
39. Bowton DL, Goldsmith WM, Haponik EF. Substitution of metered-dose inhalers for hand-held nebulizers: success and cost savings in a large, acute-care hospital. Chest 1992;101(2):305–308.
40. Turner MO, Gafni A, Swan D, FitzGerald JM. A review and economic evaluation of bronchodilator delivery methods in hospitalized patients. Arch Intern Med 1996;156(18):2113–2118.
41. Tenholder MF, Bryson MJ, Whitlock WL. A model for conversion from small volume nebulizer to metered dose inhaler aerosol therapy. Chest 1992;101(3):634–637.
42. Karpel JP, Aldrich TK, Prezant DJ, Guguchev K, Gaitan-Salas A, Pathiparti R. Emergency treatment of acute asthma with albuterol metered-dose inhaler plus holding chamber: how often should treatments be administered? Chest 1997;112(2):348–356.
43. American Association for Respiratory Care. Aerosol consensus statement—1991. Respir Care 1991;36(9):916–921.
44. Camargo CA, Jr, Woodruff PG. Management of acute asthma in US emergency departments: the Multicenter Asthma Research Collaboration (abstract). Am J Respir Crit Care Med 1998;157(4 Pt 2):A623.

Aerosolized Drugs: Current Regulatory Perspective

Nancy Chew MS RAC

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The Ban on Ozone-Depleting Substances
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[Respir Care 2000;45(6):764–768] *Key words: aerosol, regulation, regulatory, ozone, FDA, chlorofluorocarbon, metered-dose inhaler.*

Introduction

The regulation of aerosolized drugs is complicated by unique clinical trial issues, inherent pharmaceutics and device design challenges, and multiple regulatory jurisdictions. This article presents a selection of important regulatory topics, neither complete nor exhaustive by any means. They were selected for their interest to the clinical research and the clinical care communities.

In 1999, the United States Food and Drug Administration (FDA) published a voluminous proposal for the regulation of ozone-depleting substances (ODS). The weight given to this topic herein has more to do with the newness of the information than with its relative importance.

Who Are the Regulators?

Many governments implement laws by regulations and establish regulatory authorities to administer these regulations. Examples of regulatory authorities that affect aerosol inhalation products include the Committee for Proprietary Medicinal Products of the European Agency for the Evaluation of Medicinal Products, the Medicines Control Agency (United Kingdom), the Health Protection Branch of Health Canada, the FDA, and the United States Environmental Protection Agency (EPA).

Internationally, the United Nations was instrumental in organizing the parties to the Montreal Protocol on Ozone-Depleting Substances. The Montreal Protocol mandates the eventual complete ban on the production of ODS. The parties to the Montreal Protocol hold working group and formal meetings to discuss and approve policy. More than 160 nations have signed this treaty, and its regulatory implementation is carried out by the local regulatory authorities from these countries. In the United States, the EPA is responsible for implementing the Montreal Protocol.

The FDA is the regulatory authority mandated with implementing, inter alia, the federal Food, Drug and Cosmetic Act and the Safe Medical Devices Act. The United States EPA implements the Clean Air Act, including the manufacture and use of chlorofluorocarbons (CFCs). The FDA regulates all drugs, including aerosols using CFC propellants in self-pressurized containers. Under the Clean Air Act, the FDA (in consultation with the EPA) is required to determine whether the use of an ODS substance in an FDA-regulated product is essential.

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Within the FDA, the Center for Drug Evaluation and Research (CDER) is responsible for all aspects of the drug that is aerosolized. The device used to administer the drug is regulated by the Center for Devices and Radiological Health. Nebulizers, hand-held aerosol generators, spacers, metered-dose inhalers (MDIs), and dry powder inhalers (DPIs) are all approved generically by the Center for Devices and Radiological Health. However, DPIs and MDIs cannot be marketed without containing a drug, and each drug delivered by the device presents its own set of unique challenges. When a drug product includes delivery via MDI or DPI, the inhalers are integral to drug delivery. Dose uniformity, particle size distribution, and compatibility of the formulation with the inhaler device are all-important to CDER's drug regulation concerns. Thus, although an MDI or DPI may be approved for marketing, it is approved for marketing to the producer of the finished drug product, whose responsibility it is to demonstrate quality, purity, and potency.

The Ban on Ozone-Depleting Substances

Environmental Concerns

CFCs are stable, nonflammable, and have a low toxicity. These qualities make them ideal for many industrial uses. In addition, the fact that they don't break down is a benefit for many applications; however, CFC devastates stratospheric ozone. CFCs are neither dissolved nor broken down at the earth's surface, and they rise 10–20 miles above the earth into the stratosphere, where they linger for about a century. Although CFCs are virtually indestructible by normal environmental conditions, the harsh radiation of the stratosphere slowly decomposes the CFCs, releasing atomic chlorine. The chlorine destroys ozone. The stoichiometry of the reaction is such that one chlorine atom destroys more than 100,000 ozone molecules.

As its first cutback on CFCs, the United States government banned their use as aerosol propellants in the 1970s. However, industrial use of CFCs as refrigerants, solvents, and foam-blowing agents (in plastic manufacturing) continued.[1]

Medical Concerns

Depletion of the ozone layer has the direct negative health effect of increasing the rate of skin cancer due to reduction of the ultraviolet light shield provided by ozone. A United Nations study estimated that a 1% decrease in the atmospheric ozone concentration translates into a 2% increase in the rate of nonmelanoma cancer, which can be fatal. The United Nations sponsored the Montreal Protocol, calling for a general ban on CFC production in industrialized countries by January 1996. Developing countries have an additional 10 years to stop making CFCs.[1]

FDA Involvement

Use of CFCs is exempt from the ban called for by the Montreal Protocol when included in essential medical devices, including MDIs.[1] In an Advance Notice of Proposed Rulemaking promulgated on March 6, 1997, the FDA proposed to phase out medical products containing CFCs once three conditions are met:

1. Acceptable treatment alternatives exist for the particular MDI or other drug product so that each patient can find a product that meets his or her medical needs;
2. The alternatives are marketed for at least one year and are accepted by patients; and
3. The supply of alternative products is sufficient to ensure that there will be no drug shortages.

The FDA received 9,596 comments on the 1997 Advance Notice of Proposed Rulemaking, more than almost any other proposal in the history of the FDA. Nearly half the comments expressed general opposition to the phase-out of CFC MDIs. Many pointed out the minimal contribution of CFCs by MDIs, many described problems switching between products, and still many others asked the FDA not to remove MDIs until alternatives become available. The comments are addressed in detail in the Federal Register.[2]

In September 1999, the FDA proposed an amended regulation that set standards to be used in determining when an ODS in an FDA-regulated product is essential under the Clean Air Act.[2] Of significance is the change to the language, "use of a CFC as a propellant in a self-pressurized container." The 1999 proposed rule expands the product categories to include any food, drug, device, or cosmetic that is, is contained in, or consists in part of, an aerosol product or other pressurized dispenser that releases an ODS.

Determining Essential Use

The proposal is to use a moiety-by-moiety (rather than therapeutic class) approach to determine whether the use of an ODS in a medical product remains essential. (An active moiety is the part of a drug that makes the drug work the way it does. Many drug products may be marketed with the same active moiety.) This presents a regulatory challenge, as there are no set rules. It also de facto retards the move away from presently-used ODS-containing drug formulations.

Table 1. Proposed Rules for Changing "Essential Use" Status of Human Drugs for Oral Inhalation

Condition for Action on ODS*-Containing Products	Requirement	Rationale/Purpose for Requirement	Comment
Removal from FDA's essential use list	No longer marketed or no longer marketed in an ODS formulation	Failure to market indicates nonessentiality	None
Continued essentiality: one product containing the active moiety is marketed in one strength	1. Non-ODS product with the same active moiety is marketed with the same route of administration for the same indication and approximately the same level of convenience of use, and 2. Supplies and production capacity for the alternative(s) exist at levels sufficient to meet patient needs, and 3. At least one year of post-marketing experience exists, and 4. Patients who medically require the ODS product are adequately served by available alternatives	To comply with Clean Air Act and Montreal Protocol	Must be currently marketed
Continued essentiality: active moiety is marketed under more than one NDA, or in multiple strengths	At least two acceptable non-ODS alternatives per active moiety are marketed	ODS products marketed at distinctly different strengths will need to be replaced by non-ODS products of the same active moiety at more than one strength	"Acceptable non-ODS alternative" products must meet the four criteria listed for one product of one active moiety of one strength
Legal status of a product not specified in the FDA essential use list	Change terminology from "adulterated and misbranded" to "non-essential"	Highlights FDA's authority under Clean Air Act. De-emphasizes Federal Food and Drug Act and drug law language	A non-essential ODS product is still adulterated and misbranded under the Federal Food, Drug, and Cosmetic Act
Criteria necessary for adding a new essential use to the FDA essential use list	Compelling evidence that establishes the truth of the matter asserted. The evidence should be detailed and capable of scientific analysis and discussion	It is inappropriate to add new essential uses because of the relatively near-term phase-out of the production and importation of all ODSs	Compelling evidence must show substantial technical barriers to formulating without ODSs, the product will provide an unavailable, important public health benefit, and the use of the product does not release cumulatively significant amounts of ODS into the atmosphere

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*ODS = ozone depleting substance. FDA = United States Food and Drug Administration. NDA = New Drug Application.

The FDA proposes to list separately each currently marketed active moiety designated as essential. The 1999 proposed rule also intended to remove "essential use" designations for products no longer marketed (including metered-dose nitroglycerin) and for metered-dose steroid human drugs for nasal inhalation.

Table 1 presents the proposed "essential use" standards. In setting these standards, the FDA incorporated much of the comment information received following the 1997 Advance Notice of Proposed Rulemaking. Particular concerns include the continued availability of acceptable products (those that have the same effectiveness and roughly the same ease of use) and adequate consideration of patients who now require ODS products.

Presently, only 16 marketed prescription or active moieties use CFCs in MDIs. Only one generic product (albuterol) has been approved.

Regulatory Challenges in New Aerosol Product Development

Several important regulatory issues are involved in the development of aerosolized drug products. These can be outlined as follows.

Chemistry, Manufacturing, and Controls Complexity

Demonstrating particle size distribution, content uniformity, dose-to-dose variability, and dry powder aggregation

are among the CDER requirements. Design quality, robustness, and factors that may concern human ability to use the device are concerns of the Center for Devices and Radiological Health. The complexity of developing adequate chemistry, manufacturing, and control data has slowed development of new aerosol formulations. The FDA has issued specific guidance on the chemistry, manufacturing, and controls data required for MDIs and DPIs.[3]

The development of chemistry, manufacturing, and controls information to support a new drug product always includes:

- Characterizing the active moiety and development of validated analytical methods to assure its identity, strength, quality and purity;
- Testing the drug product for stability;
- Developing and validating quality control testing and manufacturing and procedures; and
- Ensuring the identity, strength, quality, purity, and bioavailability (including, for example, specifications for sterility, dissolution rate, and testing the container closure system for compatibility with the drug, as well as integrity).

The environmental impact of the manufacture and sale of the proposed product also must be addressed (21CFR* 314.50[d][1]iii).

For aerosolized medications, particle size distribution, fine particle mass, content uniformity, and the effects of new excipients are particularly important. Demonstrating compatibility of the formulated drug product and the container closure system can present unexpected challenges; for example, electrostatic charge developed during aerosol generation may affect dose uniformity.

Toxicological and In Vitro Modeling

Many technical issues involved in developing nonclinical models are addressed by other authors in this issue of RESPIRATORY CARE. From a regulatory perspective, demonstration of safety is fundamental to the drug approval process. Defining drug safety ordinarily includes administering very high doses of the test drug to animals to find the toxic dose and demonstrate its pathology. Typically, toxicology studies are done to support acute and chronic use, carcinogenicity potential, and any toxicities related to the mode of administration. Absorption, distribution, metabolism, and excretion are studied to provide pharmacokinetic links between animal and human studies. Additionally, drug effects on reproduction and fetal development must be studied (21CFR 314.50[2]).

To study the toxicology of aerosolized medication formulations, the practicalities of drug administration as well as issues surrounding systemic bioavailability of locally-acting drugs must be addressed.[4] Lung deposition in animals that are anatomically different from humans creates uncertainty about the delivered dose. Using an aerosol generator different from that intended for the drug product will introduce variability in both delivered dose and biocompatibility. Materials leeched or extracted from the dosing apparatus may cause adverse reactions in patients with hyperactive airways.[4] Introduction of a new propellant or excipient requires toxicity studies of the new excipient alone as well as in the delivered drug formulation.

Clinical Trial Issues

Clinical data required to support an application for approval to market a drug includes human pharmacokinetics and bioavailability (21CFR314.50[3]), clinical pharmacology studies, and controlled and uncontrolled clinical studies, and all evidence supporting the effectiveness and safety of the drug must be summarized (21CFR314.50[5]). The FDA has published guidance specifically for the evaluation of bioavailability and bioequivalence for nasal aerosols and sprays[5] and the documentation of in vivo bioequivalence of albuterol inhalation aerosols (MDIs).[6]

Establishing reliable functional clinical end points, such as forced expiratory volume in the first second or peak flow, may be possible for β-adrenergic agonists but can be difficult with corticosteroids. Demonstrating the bioequivalence of aerosolized corticosteroid drug products is complicated by the pharmacodynamics of steroid medication, the highly variable responsiveness of the lung from one patient to another, and the effects of long-term steroid use on the hypothalamic-pituitary-adrenal axis.

The FDA has issued points to consider in the clinical development programs for MDI and DPI products.[7] In developing comparability data between ODS-containing and non-ODS-containing products, the FDA's recommendation is to conduct three-armed clinical trials comparing the ODS product, the non-ODS product, and a non-ODS placebo. Properly constituting a bronchodilator placebo for use by patients who are accustomed to the taste of the active ingredient is particularly difficult.

Pediatric Concerns

Recently, CDER has actively sought clinical data to support claims for pediatric drug use. Historically, because pediatric patients were considered a protected class for ethical purposes, clinical trial data were not developed for pediatric patients. Supported by pediatricians and parental groups, the FDA issued regulations[8] and established guidelines for the Content and Format for Pediatric Use Supplements[9] and for conducting pharmacokinetic studies in support of pediatric indications—General Considerations for Pediatric Pharmacokinetic Studies.[10]

*CFR = United States Code of Federal Regulations.

One interesting difference is the use of population bioequivalence for these studies. The requirements of the Food and Drug Modernization Act, that special populations be considered in clinical trials, has spawned the advent of FDA interest in population pharmacokinetics.[11] Whereas a classic bioequivalence study compares the safety and efficacy of two products in the same patient, the population bioequivalence approach relies on data from large groups of patients, each given one product long-term.[12]

Summary

By understanding the way the regulatory concepts of safety and effectiveness are interpreted by CDER, especially by the Division of Pulmonary Drug Products, value can be added to the data developed. Keeping regulatory requirements in mind during early product development aids rapid evaluation of aerosol drug candidates and can lead to more efficient decisions about further development. Health care practitioners, the medical research community, and patient advocates can and do have a voice in the development of new regulations.

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REFERENCES

1. Nordenberg T. CFC-free medication for an ailing ozone layer. FDA Consumer Magazine (May-Jun 1997). http://www.fda.gov/.
2. US Department of Health and Human Services. Food and Drug Administration. Proposed Rule: Use of ozone-depleting substances: essential use determinations. Federal Register, Wednesday, Sept 1, 1999;64(169): 47720–47741.
3. US Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research. Draft Guidance for Industry: Metered dose inhaler (MDI) and dry powder inhaler (DPI) drug products: chemistry, manufacturing, and controls documentation. Oct, 1998. http://www.fda.gov/cder/guidance/index.htm.
4. DeGeorge JJ, Ahn CH, Andrews PA, Brower ME, Choi YS, Chun MY, et al. Considerations for toxicology studies of respiratory drug products (review). Regul Toxicol Pharmacol 1997;25(2):189–193.
5. US Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research. Draft Guidance for Industry: Bioavailability and bioequuivalence studies for nasal aerosols and nasal sprays for local action. Jun, 1999. http://www.fda.gov/cder/guidance/index.htm.
6. US Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research. Office of Generic Drugs. Interim guidance for documentation of in vivo bioequivalence of albuterol inhalation aerosols (metered dose inhalers). Jan 27, 1994.
7. US Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research. Points to consider: clinical development programs for MDI and DPI drug products. Sept 19, 1994.
8. US Department of Health and Human Services. Food and Drug Administration. Final Rule: Regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients. Federal Register Wednesday, Dec 2, 1998; 63(231): 66632–66672.
9. US Department of Health and Human Services. Food and Drug Administration. Pediatric Subcommittee of the Medical Policy Coordinating Committee. Center for Drug Evaluation and Research in Collaboration with the Center for Biologics Evaluation and Research. Guidance for Industry: Content and format for pediatric use supplements. May, 1996; Available on the internet and by Fax on Demand. http://www.fda.gov/cder/guidance/index.htm.
10. US Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research. Draft Guidance for Industry: General considerations for pediatric pharmacokinetic studies for drugs and biological products. Nov, 1998. http://www.fda.gov/cder/guidance/index.htm.
11. US Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research. Guidance for Industry: Population pharmacokinetics. Feb, 1999. http://www.fda.gov/cder/guidance/index.htm.
12. US Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research. Draft Guidance for Industry: Average, population, and individual approaches to establishing bioequivalence. Aug, 1999. http://www.fda.gov/cder/guidance/index.htm.

Aerosol Therapy Past, Present, and Future: A Clinician's Perspective

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[Respir Care 2000;45(6):769–776] *Key words: aerosol, metered-dose inhaler, nebulizer, dry powder inhaler.*

Introduction

The publication of the Consensus Statement on Aerosols and Delivery Devices in this issue of RESPIRATORY CARE is very timely, as it provides a summary of progress in the field of aerosol therapy to the end of the 20th century and affords us an opportunity to look forward. The publication of this document also occurs at the cusp of an age during which devices were developed empirically, with little understanding of how they would perform in clinical practice, and that of an era in which delivery systems will be designed to perform specific functions and whose performance characteristics are known before they are brought to the market. During the second half of the 20th century, aerosol therapy has become established as a valuable means of treating pulmonary disease. However the full potential of this form of therapy has not been realised, largely because the most widely prescribed device, the pressurised metered-dose inhaler (pMDI), utilises 45-year-old technology, remains difficult to use *effectively* and, most importantly, is being used for purposes for which it was never intended

Why Use the Inhaled Route for Pulmonary Disease?

Aerosol therapy is considerably more complex than oral therapy, since drug must be delivered to an organ specifically evolved to exclude foreign material. A patient with cystic fibrosis may swallow 10 or more pancreatic supplement capsules as a single bolus, but to deliver 20 μg of drug to the lungs *reliably* and *reproducibly* is extremely difficult. The complexities and difficulties involved in delivering drug reliably to the lower airways are such that the benefits derived from this mode of delivery must be considerable to justify the effort expended. Therefore, it is worth recalling why the inhaled route is used when treating pulmonary disease. The principal reasons are:

- A more rapid onset of action for drugs such as β agonists.

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• An improved "therapeutic index." That is, for a given therapeutic effect the potential for systemic effects is minimised.

• The ability to deliver drugs that are not effective when administered orally.

Speed of Onset

The original portable inhaler was the asthma cigarette.[1] This effective delivery system was used for more than 100 years to administer anticholinergic agents and, with the inclusion of nicotine, the asthma cigarette was probably the only delivery system to be developed that directly encouraged compliance. The cigarette was used because it was available, rather than having been designed for a particular purpose; this use of an existing delivery system rather than developing a purposely-designed system was echoed 160 years later when the pMDI was used to deliver inhaled steroids. Unpredictable drug delivery and unacceptable side effects eventually led to the demise of the asthma cigarette.

Adrenaline was first inhaled in the 1920s, and subsequently sympathomimetic agents were administered via injection or via portable, but inconvenient, glass bulb nebuliser. These were replaced more than 44 years ago by the more convenient, multi-dose, portable pMDI. The great advantage of using the inhaled route for drugs designed to relieve symptoms is that the onset of action can be rapid, the benefits of inhaled sympathomimetic agents being observed in minutes. The same therapeutic effects can be achieved administering the drugs orally, but maximal bronchodilation is only achieved some hours later and is accompanied by substantial systemic effects.[2]

Though important, short-acting β agonists are simply a means of providing rapid relief from symptoms, and ideally they would not be required at all, in that their use represents the failure of preventative therapy. Patients require bronchodilators in two settings. Most commonly they are used to provide relief of intermittent symptoms on the background of poor, moderate, or even good control. In this context, β agonists are effective and generally delivered at nominal doses that ensure supramaximal lung doses, even with poor technique. If bronchodilation is inadequate because of poor technique, the patient receives immediate feedback and will take further doses.

During acute exacerbations, responses to β agonists are blunted and much larger doses are required.[3] It is clear that these high doses can be delivered effectively via pMDI with holding chamber, conventional jet nebuliser, and, indeed, by some dry powder systems. There are many who argue that jet nebulisers are not required for asthma therapy, and, indeed, there are no settings in which other delivery systems cannot be used.

Improved Therapeutic Index

The improved therapeutic index derived from inhaling medication to treat pulmonary disease applies to a variety of drug groups, including bronchodilators, corticosteroids, and antibiotics such as aminoglycosides. Though there is endless debate regarding the safety of inhaled steroids, agents, it should be remembered the "epidemics" of asthma deaths experienced in a number of countries in the 1960s resulted from the use of the relatively nonselective agonist isoprenaline (known as isoproterenol in North America) at high doses.[4,5] Asthma deaths are most frequent in the elderly, but during the "epidemic" of the 1960s, many of the excess deaths were in young patients. The modest improvement in asthma mortality noted in some countries in the last decade[6] does not compensate for the numbers affected during the "epidemic" years. The use of high-dose inhaled sympathomimetic agents administered via nebuliser to the elderly who may have significant ischaemic heart disease remains a cause for concern.

Factors influencing the therapeutic index include class of drug, type of drug within that class, and the delivery system chosen. Inhaled therapy is used to deliver drugs such as corticosteroids, as it may maximise the "therapeutic index." However, to view aerosol therapy as the "safe way" to deliver corticosteroids is not sufficient. To maximise the therapeutic index, inhaled steroids must be delivered in

• a device/drug combination designed to maximise therapeutic effect and minimise side effects, and

• the lowest effective dose.

Inhaled corticosteroids have many beneficial effects, including reduced daytime and nighttime symptoms (day-to-day bother), reduced exacerbations, reduced hospitalisation rates, reduction in bronchial hyper-responsiveness, which continues to improve even 2 years after commencing treatment, and apparently healthier airways, as assessed by lung biopsy.[7–9] The widespread use of inhaled corticosteroids in some countries is believed to have contributed to a reduction in mortality rates amongst younger patients.[5] It is also claimed that they may alter the natural history of the disease, but this hypothesis is far from proven. The recent United States Food and Drug Administration statement regarding the safety of inhaled steroids[10] reminds us that the use of such agents may lead to significant adverse effects and that the potential for such effects should be minimised by applying the above principles.

The United States Food and Drug Administration cites a few short-term trials using an inefficient dry powder inhaler (DPI) to deliver beclomethasone to children at a fixed dose. These trials showed an apparent small but temporary effect on growth immediately after the introduction of the inhaled steroids. The fact that an effect can be observed is not too surprising, as the delivery system/

drug combination is likely to have a poor therapeutic index. Oropharyngeal deposition with this device will be high, in excess of 70%, of which 20% or more will reach the systemic circulation, whereas the pulmonary dose may be 10% of the nominal dose if used well, but is probably significantly less in many patients. Therefore, more than half of the systemic effect will result from the swallowed dose. The only other device with such a poor systemic-to-therapeutic ratio is a conventional suspension beclomethasone pMDI, and recognition of this led to the development of holding chambers. The therapeutic index can be significantly improved by delivering drugs such as beclomethasone or budesonide via a device that minimises upper airways deposition, such as a pMDI with holding chamber or a relatively efficient dry powder device.[11,12] The safety profile of the novel solution-based pMDI is still being appraised and is likely to be safer than previous suspension-based formulations, as pulmonary deposition is significantly greater than oropharyngeal deposition. However, the development of this delivery system has only served to highlight how little we know regarding the lung sites to which drugs such as inhaled steroids should be directed.

Drugs with minimal oral availability may also represent a safer option, with the proviso that the lowest effective dose must be used. Simply delivering inhaled steroids efficiently to the lung or using inhaled steroids that do not reach the systemic circulation if swallowed is not sufficient to ensure safety with current steroids, as the total lung dose will be absorbed and reach the systemic circulation. Increasing the delivered dose may provide little additional therapeutic benefit but will certainly increase the systemic exposure. There is a worrying tendency for some patients and clinicians to use higher and higher doses of steroids not absorbed via the gastrointestinal tract, under the mistaken belief that these are "safe" steroids. However, current inhaled steroids are effectively absorbed from the lungs and, therefore, the risk/benefit ratio can only be optimised by using the *lowest dose that works*. One possible confounding factor is that the dose required to optimise the prevention of exacerbations may be higher than that needed to minimise symptoms, but there is little evidence at present to answer this question.

It is interesting to note that, on the one hand, the regulatory authorities noted that inhaled corticosteroids can produce measurable systemic effects in certain circumstances and, on the other hand, they promote the concept of "equivalence" to ensure that future devices perform in a similar manner to those currently available.

Currently there are no long-term data to back up the concept that the use of inhaled steroids has any effect on final height, and, indeed, to date, final height data from countries with high inhaled steroid usage have been very reassuring.[13]

1970–2000: An Era of Relative Under-Achievement

Device Issues

As noted above, there was steady progress in inhaled therapy in the first half of the 20th century, until the mid-1950s when the pMDI was developed for a very specific purpose, which was to provide a convenient, portable, multi-dose device for delivering bronchodilators whenever and wherever they were required. Unfortunately, when the next major therapeutic advance was made, in the late 1960s, with the development of an inhaled corticosteroid, the decision was made to use an existing delivery system, the pMDI. This historical accident had profound effects on asthma therapy during the subsequent 30 years, with pharmaceutical companies coming to believe that it was desirable to use the same type of delivery system for both β agonists and inhaled steroids. It should be acknowledged that the specifications of an ideal delivery system for inhaled steroid were not known in the 1960s, but they were known in the late 1980s, when the pharmaceutical companies elected to perpetuate the failings of the pMDI and develop replacements for the chlorofluorocarbon (CFC) propellants rather than develop novel devices appropriate to the latter part of the 20th century. Every other industry faced with the loss of CFCs discovered that this enforced change resulted in the development of much more effective alternatives, to the benefit of both the manufacturers and consumers. Unfortunately, the pharmaceutical industry chose to take what has proven to be the most difficult option and has invested over a billion dollars to preserve the pMDI. Furthermore, they have chosen, in all but one case, to opt for "equivalence" when developing CFC replacement pMDIs; that is, the hydrofluoroalkane-propelled device should be as inefficient as the previous device. Certain improvements have been made, such as improved metering valves, but these can be likened to placing a catalytic converter on a 1950s family Ford and calling it the vehicle for the 21st century.

The greatest problem with pMDIs is that, although they are perceived to be convenient and easy to use, they are extremely difficult to use *effectively*—the most common problems being failing to shake the device (which may reduce drug delivery by up to 50%), poor coordination, rapid inhalation, or failing to inhale because of the cold FREON effect.[14,15] These problems were known to exist more than 20 years ago, when holding chambers,[16] spacing devices, and breath-actuated devices were devised to overcome some of them, such as coordination difficulties and high oropharyngeal deposition.[17] These devices, which were designed to compensate for the failings of the pMDI, have problems of their own, such as the variable static charge inside plastic spacers, but, despite the enormous literature on the subject generated by a few centres, static

is probably a relatively minor source of variability in routine practice.[18]

The ideal device for inhaled corticosteroids, and, indeed, other classes of drugs that do not need to be readily available, would be one that would be intuitive to use, would deliver reproducible quantities of drug to all areas of the lung, would deliver little or no drug to the upper airway, and would provide some positive feedback to the patient that the dose had been administered effectively. It does not have to be pocket-sized. An ideal device would mean that the respiratory clinicians would have to spend little or no time teaching correct techniques, which would permit much more time to discuss issues such as safety, fear of dependence, and the multitude of other concerns that patients may have when faced with long-term therapy and that influence compliance and outcome.

Patient-Related Factors

The benefits of inhaled steroids and other forms of preventive therapy are frequently vitiated by one or more of the "three Cs": compliance, competence, and contrivance.

• Compliance (or adherence) with a treatment regimen is a complex area and is a major problem in all therapeutic areas, including oncology, where noncompliance amongst children and others is a significant problem.[19] Compliance is poor in all age groups, including preschool children,[20] and is independent of factors such as disease severity and education. The best guide to compliance (in the absence of a data logger) is probably to toss a coin, which has been shown to be as accurate as clinician assessment.[21] The impact of poor compliance is probably more apparent in the asthma clinic than in many other areas of therapy, because patients continue to complain of symptoms and experience exacerbations, thus provoking further interaction with health care providers.[22] Fear of steroids, conflicting information from health care professionals, and lack of confidence in the delivery systems probably all have an effect, as do many other patients factors.

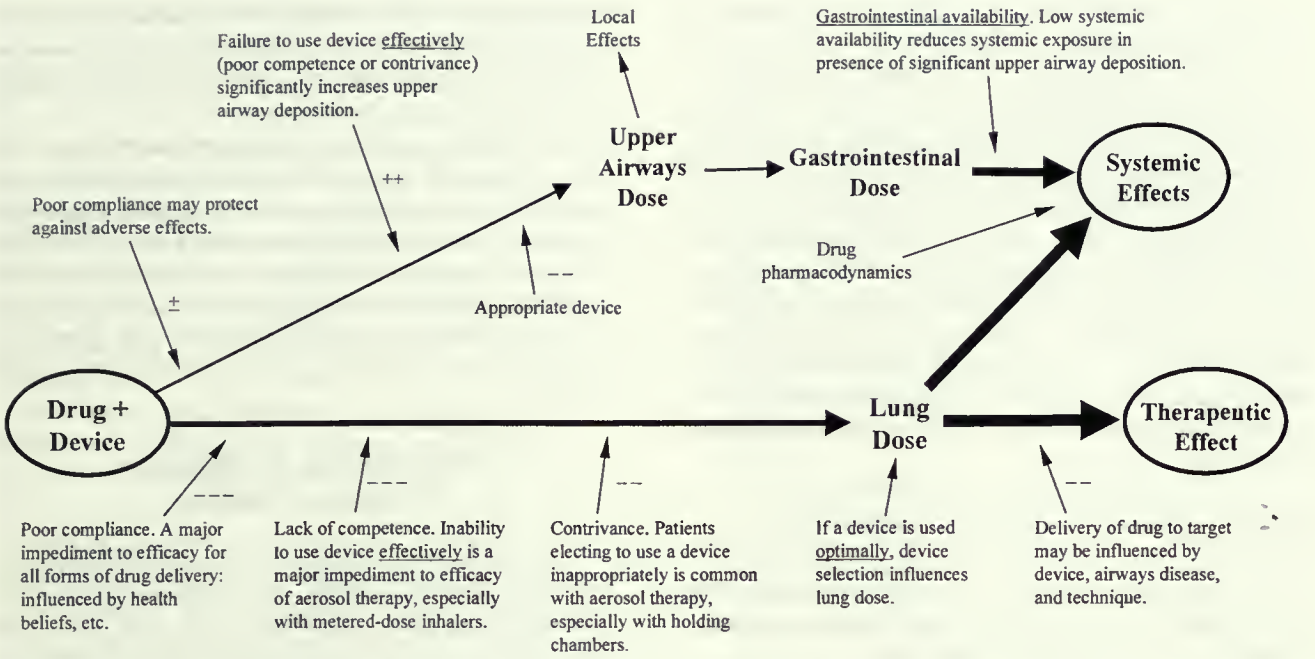
• Competence is a particular problem in the elderly,[23] largely because of cognitive problems. Problems observed, in addition to those noted above, include spraying pMDIs on the chest, failure to take the cap off the device, and difficulty actuating the device because of poor muscle strength or arthritis. In the very young, the device must be administered by the parent, and the biggest observed problem is associated with the distress induced by the therapy—delivering aerosols to crying or upset children results in little or no drug reaching the lungs.[24]

• Contrivance is also an issue affecting all age groups. Patients (or caregivers) know what they should do, but contrive to use the device in a different way because they believe it is as effective. This particularly affects pMDIs and pMDIs with holding chambers. Patients may spend a prolonged period with the respiratory therapist or other clinician, who explains why it is important to use the device in a particular way; the patient then takes a couple of doses of a β agonist using a suboptimal technique and achieves symptomatic relief since the inhaler delivers supramaximal doses. This snatched inhalation is then used when administering inhaled steroids, since the feedback from β agonist use suggests that this technique is adequate. Contrivance is a significant problem, even in preschool children. In a recent survey at our clinic, we found that 67% of parents of preschool children admitted that they regularly did not use the holding chamber, instead firing the pMDI into the child's mouth as the child breathes in, despite the fact that all of them knew this was incorrect.

Comparison with Oral Therapy

Compliance is a problem in all areas of therapy, and at present there is little to suggest that compliance is better with oral therapy than with inhaled therapy. The most widely quoted paper[25] on the subject compared prescriptions taken up for theophyllines compared with those for inhaled steroids, which indicated possibly better compliance with oral therapy; but it would be difficult to generalise from this study for many reasons, including the fact that two different classes of drugs were compared. Competence is also a problem, especially with the elderly. It has been estimated that up to half the population of a country such as the United States are functionally illiterate, meaning that they cannot understand an instruction such as "take the tablet after meals."[26] This is a particular problem in the elderly. However, the consequences of poor competence or contrivance are probably greater with inhaled therapy. If a patient complies and takes his or her oral medication, it will probably have some therapeutic effect even if it is, for example, taken inappropriately before a meal, whereas lack of competence with an inhaler may result in total failure to deliver any drug to the lower airways. Such considerations, albeit not expressed in quite that way, probably account for the relatively widespread use of jet nebulisers in the elderly, since they appear to be less operator-dependent than other delivery systems. Contrivance is a major problem with inhaled therapy, particularly with pMDIs (with or without holding chambers), but, again, oral therapy is not immune from contrivance problems (eg, patients may chew tablets that should be swallowed whole), though again the consequences of contrivance are probably greater with inhaled therapy.

The greatest impediment to achieving a therapeutic effect with a given drug is failing to take the medication at all or failing to take an amount sufficient to achieve the


Local Effects
Failure to use device effectively (poor competence or contrivance) significantly increases upper airway deposition.
Gastrointestinal availability. Low systemic availability reduces systemic exposure in presence of significant upper airway deposition.
Upper Airways Dose
Gastrointestinal Dose
Systemic Effects
Poor compliance may protect against adverse effects.
++
Drug pharmacodynamics
±
--
Appropriate device
Drug + Device
Lung Dose
Therapeutic Effect

--
--
Poor compliance. A major impediment to efficacy for all forms of drug delivery: influenced by health beliefs, etc.
Lack of competence. Inability to use device effectively is a major impediment to efficacy of aerosol therapy, especially with metered-dose inhalers.
Contrivance. Patients electing to use a device inappropriately is common with aerosol therapy, especially with holding chambers.
If a device is used optimally, device selection influences lung dose.
Delivery of drug to target may be influenced by device, airways disease, and technique.

Fig. 1. To maximize the therapeutic index, patients must be provided with a device that they can and will use effectively and use the lowest dose that provides a given therapeutic effect.

desired therapeutic effect. However, once the patient has decided to take the medication, there is a greater probability of efficacy if taken orally rather than if inhaled. The difficulties associated with the use of current inhaler devices ensure that issues of competence or contrivance can prevent effective drug delivery, even when the patient has made the decision to administer the medication (Fig. 1). Patients deserve patient-friendly, intuitive, reliable devices to maximise the potential for positive benefits.

Influence of Patient Factors on the Therapeutic Index

Competence and contrivance may not only negate the therapeutic benefit of a given drug, they may also significantly increase the risk of adverse effects. Poor technique leading to high oropharyngeal deposition adversely affects the therapeutic index by reducing the beneficial effects while increasing the gastrointestinal contribution to the systemic dose. Frequently, the nominal dose is increased in an attempt to compensate for the apparent lack of response. Similarly, contrivance can substantially adversely affect the therapeutic index. For example, failure to use a holding chamber, which is very common, may have a major impact on the therapeutic index, Therefore a further demand on the ideal device is that it should be difficult for the patient to use the device incorrectly.

Aerosol Myths

Myth 1: "Aerosol Therapy is Complex"

The basic principles of aerosol therapy are simple, but, sadly, few clinicians or other health care professionals receive any training, and even then the basic principles are generally omitted.[27]

The airways have evolved to exclude foreign material, but a relative weakness in these defenses has left us a window of opportunity, in that particles between 1 μm and 7 μm deposit relatively effectively in the lungs. Larger particles deposit in the upper airways by impaction, whereas smaller particles are exhaled (particles < 0.1 μm do deposit in the lungs relatively effectively, but carry such little drug that they are not used for aerosol therapy). Impaction in the upper airway is determined by inertia; that is, the larger the particle or the faster it is travelling, the more likely it is to impact. Particles of 1–4 μm are relatively stable in air and, therefore, deposition in the lungs can be enhanced by utilising gravity. Breath-holding allows particles longer time to settle and deposit by sedimentation.

Therefore, to maximise the chances of depositing drug in the lungs, aerosolised drug should be inhaled slowly, followed by a breath-hold to maximise the chances of drug depositing in the lungs. This is true for current pMDIs with or without holding chambers. For continuous-output nebulisers, the value of breath-holding is negated by the wasted

drug emitted during the breath-hold, and, therefore, tidal breathing is employed.

The rules are broken for current drug powder systems, because standard particles of 1–7 μm have very strong forces of attraction and, therefore, energy is required to deaggregate them into respirable-size particles. For current systems this energy is provided by compressed gas in jet nebulisers and boiling propellants (CFC or hydrofluoroalkane) in pMDIs. For dry powder systems, the energy must be provided by the patient's inspiratory effort—the harder the patient inhales, the more small particles are generated, and the effects of the increased flow are more than offset by the increase in respirable-size particles, since the likelihood of impaction is related to the velocity and the square of the diameter (VD^2).

Myth 2: "Current Devices are Good Devices"

It is difficult to envisage another type of therapy that, out of choice, uses technology that is half a century or more old. It is worth remembering that:

- Conventional jet nebulisers were devised in the 1930s.
- pMDI were developed in the 1950s.
- Dry powder systems first appeared in the 1960s.
- Holding chambers were developed in the late 1970s to overcome the shortcomings of pMDIs.

It should be noted that the concept of delivering insulin as an aerosol is not new and was explored in the 1930s, after the development of the jet nebuliser, and in the 1950s, when pMDIs were developed. The idea was soon abandoned in both cases when it was realised that neither conventional jet nebulisers nor pMDIs were able to deliver reproducible doses to the lungs.

The Need for a Journal of Irrelevant Aerosol Therapy

Though the medical literature is inundated with articles on various aspects of aerosol therapy, the net effect of these articles has been to convince the majority of clinicians that aerosol therapy is far too complex to understand. Very few of the many hundreds of articles have had a real impact on patient care, not least because they generally concentrate on technical aspects of device performance. In vitro studies should generally be regarded as a tool to be used during product development and for quality control during manufacture. The relevance of bench-top in vitro testing to real life clinical performance is generally tenuous, though improved techniques using anatomically realistic models of the upper airway and patient flow profiles have made this approach a little more relevant.[28] Even studies that involve human subjects are generally so far removed from use in real life that they are of little value other than curiosity. Gamma scintigraphy studies assessing deposition in a few extremely well trained subjects do not tell us how the device will perform when used in clinical practice. At best, they tell us the best possible performance that can be achieved.

Such studies suggest that the experts know how much drug a particular device will deliver, when in fact it is impossible with current devices to accurately predict the lung dose in an individual subject using a particular device on a given day. More importantly, the relatively high intrasubject variability means that we cannot predict the lung dose that will be achieved the following day. Moreover, we do not know what lung dose is required for a given patient.

Aerosol Delivery for Nonasthma Pulmonary Conditions

Other drugs, such as antibiotics, frequently require delivery of milligram quantities, and this limits the choice of current delivery systems. However, it has been shown that similar lung doses can be achieved using much more convenient conventional dry powder systems.[29] Patients with cystic fibrosis are burdened by multiple time-consuming therapies,[30] and a huge opportunity exists to improve their quality of life. However, because this is a relatively small patient group, it is difficult to foresee pharmaceutical companies investing large sums of money in novel delivery systems that would require new product licences, and so patients are likely to be denied these potential benefits. Such developments may be limited to very expensive novel compounds. Pressure on regulatory authorities and pharmaceutical companies from patient-centred groups may be the only way to change this situation.

How Should We Cope With Existing Technology?

If no new drugs or delivery systems were to appear in the future, we could treat pulmonary diseases such as asthma relatively effectively by *doing the simple things well*:

- Symptomatic relief therapy: provided that the patient demonstrates competence, almost any device is appropriate, and issues such as cost and patient preference should be considered.
- Inhaled steroids and other regular medication: use the lowest dose that works, using a drug/device combination that maximises the therapeutic index. Compliance, competence, and contrivance are all important in determining efficacy and adverse effects, and steps to minimise adverse effects should be an important aspect of patient care.

The Future

The field of aerosol therapy is likely to change over the coming years, but the magnitude and direction of that

change is unclear. Inhaled insulin for the treatment of diabetes appears imminent, and this is likely to have a significant impact on the whole field of aerosol therapy. Devices developed for delivering this potent peptide must deliver relatively reproducible lung doses in order to avoid adverse effects such as hypoglycaemia. This requires tight technical specification, but, more importantly, requires a device whose performance does not depend on the patient learning a difficult and complex inhalation technique. It will be interesting to observe whether there will be a need for respiratory therapists to train patients or whether the devices are felt to be so intuitive that no special training is required.

Once these requirement have been met for one potent peptide, others may also be delivered via this route. Perhaps more importantly, patients, clinicians, and possibly even regulatory authorities will demand intuitive, patient-friendly devices for asthma therapy, once they have been shown that it is indeed possible to design such devices.

Alternatively, novel noninhaled therapies in asthma, diabetes, or other conditions may draw a veil over the whole game and banish inhaled therapy to the history books. Pharmaceutical companies are therefore faced with an interesting dilemma: whether to develop new devices, at substantial cost (since new product licences will be required), for drugs such as inhaled steroids (which are or are becoming generic drugs) and risk being overtaken by potent novel therapies, or to search for novel therapies and make do with current devices. Once drugs become generic agents, an opportunity exists for other companies to improve the choice of delivery systems. However, regulatory authorities strive for "equivalence" and dictate that generic devices operate as well, or rather as badly, as the original device. Consequently, the development of effective, reproducible, intuitive, intrinsically safe, patient-friendly devices for preventative therapy in asthma may still be a little way off.

Aerosol therapy currently has changed little over the past two decades, and the stage is set for dramatic improvements during the next decade, but whether such improvements are realised will be influenced by a wide range of factors, including the advent of new forms of therapy, the attitude of regulatory authorities, and the commercial perceptions of the pharmaceutical companies.

REFERENCES

1. Sakula A. A history of asthma: the FitzPatrick Lecture 1987. J R Coll Physicians Lond 1988;22(1):36–44.
2. Webb J, Rees J, Clark TJ. A comparison of the effects of different methods of administration of beta-2 sympathomimetics in patients with asthma. Br J Dis Chest 1982;76(4):351–357.
3. Reddel H, Ware S, Marks G, Salome C, Jenkins C, Woolcock A. Differences between asthma exacerbations and poor control. Lancet 1999;353(9150):364–369.
4. Speizer FE, Doll R, Heaf P. Observations on recent increase in mortality from asthma. Br Med J 1968;1(5588):335–339.
5. Blauw GJ, Westendorp RGJ. Asthma deaths in New Zealand: who-dunnit? (editorial) Lancet 1995;345(8941):2–3
6. Campbell MJ, Cogman GR, Holgate ST, Johnston SL. Age specific trends in asthma mortality in England and Wales, 1983- 95: results of an observational study. BMJ 1997;314(7092):1439–1441.
7. van Essen-Zandvliet EE, Hughes MD, Waalkens HJ, Duiverman EJ, Pocock SJ, Kerrebijn KF. Effects of 22 months of treatment with inhaled corticosteroids and/or beta-2-agonists on lung function, airway responsiveness, and symptoms in children with asthma. The Dutch Chronic Non-Specific Lung Disease Study Group. Am Rev Respir Dis 1992;146(3):547–554.
8. Bisgaard H, Moller H. Changes in risk of hospital readmission among asthmatic children in Denmark, 1978–1993. BMJ 1999;319(7204): 229–230.
9. Laitinen LA, Laitinen A. Mucosal inflammation and bronchial hyperreactivity (review). Eur Respir J 1988;1(5):488–489.
10. United States Food and Drug Administration, Division of Pulmonary Drug Products. Class labeling for intranasal and orally inhaled corticosteroid containing drug products regarding the potential for growth suppression in children. November 9, 1998. http://www.fda.gov/cder/news/cs-label.htm. Accessed May 15, 2000.
11. Lipworth BJ. New perspective on inhaled drug delivery and systemic bioactivity (review). Thorax 1995;50(2):105–110
12. Pedesen S. Inhalers and nebulizers: which to choose and why (review). Respir Med 1996;90(2):69–77.
13. Agertoft L, Pederson S. Final height of asthmatic children treated for 7–11 years with inhaled budesonide (abstract). Am J Respir Crit Care Med 1998;157(4 Pt 2):A711.
14. Paterson IC, Crompton GK. Use of pressurised aerosols by asthmatic patients. Br Med J 1976;1(6001):76–77.
15. Thorsson L, Edsbacker S. Lung deposition of budesonide from a pressurised metered-dose inhaler attached to a spacer. Eur Respir J 1998;12(6):1340–1345.
16. Friegang B. New method of beclomethasone aerosol administration to children under 4 years of age. Can Med Assoc J 1977;117(11): 1308–1309.
17. Newman SP, Millar AB, Lennard-Jones TR, Moren F, Clarke SW. Improvement of pressurised aerosol deposition with Nebuhaler spacer device. Thorax 1984;39(12):935–941.
18. Janssens HM, Devadason SG, Hop WCJ, Le Souef PN, De Jongste JC, Tiddens HA. Variability of aerosol delivery via spacer devices in young asthmatic children in daily life. Eur Respir J 1999;13(4):787–791.
19. Davies HA, Lennard L, Lilleyman JS. Variable mercaptopurine metabolism in children with leukaemia: a problem of non-compliance? BMJ 1993;306(6887):1239–1240.
20. Gibson NA, Ferguson AE, Aitchison TC, Paton JY. Compliance with inhaled medication in preschool children. Thorax 1995;50(12): 1274–1279.
21. Braunstein GL, Trinquet G, Harper AE. Compliance with nedocromil sodium and a nedocromil sodium/salbutamol combination. Compliance Working Group. Eur Respir J 1996;9(5):893–898.
22. Milgrom H, Bender B, Ackerson L, Bowry P, Smith B, Rand C. Noncompliance and treatment failure in children with asthma. J Allergy Clin Immunol 1996;98(6 Pt 1):1051–1057.
23. Armitage JM, Williams SJ. Inhaler technique in the elderly. Age Ageing 1988;17(4):275–278.
24. Everard ML. Delivering aerosolised drugs to distressed children is a thankless task. Arch Dis Child 2000;82:428.

25. Kelloway JS, Wyatt RA, Adlis SA. Comparison of patients compliance with prescribed oral and inhaled asthma medications. Arch Int Med 1994;154:349–351.
26. Health literacy: report of the Council of Scientific Affairs. Ad Hoc Committee on Health Literacy for the Council of Scientific Affairs, American Medical Association. JAMA 1999;281(6):552–557.
27. Hanania NA, Wittman R, Kesten S, Chapman KR. Medical personnel's knowledge of and ability to use inhaling devices: metered-dose inhalers, spacing chambers, and breath-actuated dry powder inhalers. Chest 1994;105(1):111–116.
28. Everard ML, Dolovich M. In vivo measurements of lung dose. In: Drug delivery to the lung: clinical aspects. Bisgaard H, O'Callaghan C, Smaldone G, editors. (In series 'Lung biology in health and disease'). In press.
29. Goldman JM, Bayston SM, O'Connor S, Meigh RE. Inhaled micronised gentamicin powder: a new delivery system. Thorax 1990; 45(12):939–940.
30. Smith G. A patient's view of cystic fibrosis. J Adolesc Health Care 1986;7(2):134–138.

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Books, Films, Tapes, & Software

Cardiopulmonary Anatomy and Physiology: Essentials for Respiratory Care, 3rd edition. Terry Des Jardins MEd RRT. Albany: Delmar Publishers. 1998. Soft-cover, illustrated, 437 pages, $45.95.

The author of this text, Terry Des Jardins, brings a wealth of experience to the teaching of basic science to respiratory care students. In the forward to this, the third edition of the text, Dr Thomas DeKornfield identifies the two major problems confronted by respiratory care educators in dealing with the anatomy and physiology of the cardiopulmonary systems: first, most introductory physiology courses cover these systems too superficially to provide respiratory care students with the background they need, and second, anatomy and physiology presented at a relatively advanced level without being placed in a clinical context is very difficult for students to absorb. Des Jardins confronts these two problems head-on by using a highly systematic approach to complex material and by placing that material within a clinical context wherever possible. All but four of the 16 chapters contain specific clinical applications sections.

The table of contents provides a detailed guide to the book's structure. While it does not use Roman numerals, letters, or numbers, the book is actually arranged in a typical outline format. The arrangement of headings and subheadings seen in the table of contents is carried into the text chapters, although this breaks down in a few places (eg, the beginning of Chapter 2). Also, each chapter begins with an exceptionally comprehensive set of objectives (sometimes stretching to several pages). Key words in the objectives are emphasized in the text by placing them in color, and these same key words are defined in the glossary at the end of the book, again using the same color coding. This is just one example of the exceptionally effective use of color in this text (previous editions were entirely in black and white).

In the preface, Des Jardins points out that a clear understanding of function (physiology) cannot be achieved without a comprehensive knowledge of structure (anatomy). Hence, Chapter 1 is devoted to a detailed presentation of the anatomy of the respiratory system. A good indication of any textbook's effectiveness is how well it handles the most complex and difficult topics. In the respiratory system, the 3-dimensional anatomy of the larynx is one of these difficult topics. Des Jardins devotes 5 full pages and 4 color figures to this structure, giving one of the most comprehensive and clear presentations I have seen. Figures are generously scattered throughout the chapter and are exceptionally well done. Although they are little changed from those in the second edition, the addition of color adds immeasurably to the information conveyed. Also, not all figures are done to the same degree of detail; rather, each has just enough detail to convey the necessary information without being overly busy. The use of shading rather than solid color is particularly useful. As with the figures, the text is little changed from the second edition; however, it is clear, concise, easy to read, and vocabulary and sentence structure seem appropriate to the intended audience of beginning respiratory care students. All the chapters end with 10 to 20 multiple-choice review questions.

Chapters 2 through 10 present the essentials of respiratory physiology and the anatomy and physiology of the cardiovascular system. Both the text and figures are virtually identical to those found in the second edition, but again, all topics are presented concisely and with great clarity. A number of the diagrams in these chapters are highly complex. Des Jardins comments on this in the preface to the effect that these diagrams are similar to those found in the scientific literature (thus students should become accustomed to them), and they are needed to illustrate the complex interactions that are a fact of life in respiratory physiology. As complex as they might be, all will yield to students' understanding with careful, systematic explanation by the instructor, and many of these will be exceptionally useful as transparencies during lecture.

As in Chapter 1, particularly important and difficult topics are carefully and completely analyzed and discussed. For example, Chapter 2 has an excellent section that illustrates spirograms for a number of pathologic breathing patterns and describes their effects on gas exchange. This is extremely helpful for students, and to my knowledge is unique to this text. Des Jardins also emphasizes the importance of Poiseuille's law and its consequences in pulmonary and cardiovascular pathophysiology (Appendix 3 is also devoted to this topic). Each chapter in this section of the text ends with the presentation of two clinical cases. Each case is carefully laid out with appropriate physical findings and lab and radiograph data. These findings are then carefully analyzed within the context of basic physiology. Following this analysis, therapeutic interventions are described, and the reasons for the success of the interventions are also analyzed within the context of basic physiology.

Following Chapter 3, on diffusive gas exchange, Chapter 4 presents the basics of pulmonary function testing, a topic that most beginning respiratory care students find obscure and impenetrable. The chapter is systematic, with each concept building logically upon the next. Des Jardins' presentation of flow-volume loops and the relationship between these and various forced expiratory flow measurements is outstanding. The major strength of the diagrams in this chapter is how they manage to combine several major concepts into one visual presentation.

Chapters 5 and 6 focus on the circulatory system: Chapter 5 on cardiovascular anatomy and physiology, and Chapter 6 on hemodynamic measurements. Typical hemodynamic measurements encountered by respiratory therapists working in critical care (eg, central venous pressure, wedge pressure, cardiac index) are all carefully explained and exceptionally well illustrated. Again, physiology parameters are effectively correlated with clinical findings.

Chapter 7, on oxygen transport, has several major strengths. It carries out a thorough analysis of the consequences of both the position and *shape* of the hemoglobin-oxygen dissociation curve. Likewise, the important relationship between oxygen transport and oxygen consumption is analyzed thoroughly, and pulmonary shunting and its consequences are clearly covered.

Without question, one of the strongest parts of this text is its treatment of carbon dioxide transport and acid-base balance (Chapter 8). This topic is presented in its full complexity, but with great clarity. Typical acid-base disturbances are fully described, and the use of the P_{CO_2}/HCO_3^-/pH

nomogram, both as a mechanism to understand acid-base balance and as a clinical tool, is done with great effectiveness. For the student, the complexities of this topic will yield to careful study and good explanations by the instructor.

Chapter 9 presents the topic of the ventilation-perfusion ratio ($\dot{V}/\dot{Q}$) relationship. Again, a rather complex topic is presented clearly, but without apology for its complexities. Des Jardins uses the O_2–CO_2 diagram first developed by Rahn and Fenn in the 1960s to present this topic. Two somewhat unusual and particularly dramatic cases are presented to illustrate clinical correlations.

Perhaps the least understood topic in the arena of respiratory physiology is the control of ventilation (Chapter 10). This chapter presents the basics, but also reflects the lack of cohesive understanding that characterizes this area of respiratory physiology. The clinical case presented in this chapter would have fit better in Chapter 8 (acid-base balance), and the addition of the material on adaptation to high altitude was somewhat confusing and would have fit better in Chapter 15 (cardiopulmonary adaptations to high altitude).

The remainder of this text (Chapters 11 through 16) presents the changes in the respiratory system that occur under special and unusual circumstances (fetal life, renal failure, aging, exercise, high altitude, and high pressure). These chapters are both interesting and informative, and add a much needed dimension to basic respiratory care education. Chapter 11, on fetal/newborn physiology, is concise, yet especially informative. Chapter 12, on renal failure, suffers from an insufficient presentation of basic renal anatomy and physiology. The factual consequences of renal failure are presented; however, they are not put in the same clear anatomical and physiologic context that characterizes the rest of the book.

Chapter 13 outlines basic changes in the cardiopulmonary system that are a part of the normal aging process—information that will become increasingly important as our population ages and respiratory care moves more into the chronic and subacute arenas. To my knowledge, no other text used commonly in respiratory care has this material presented in a single location. Chapter 14 (effects of exercise on cardiopulmonary physiology) gives an excellent overview and ends with a short section on cardiovascular rehabilitation. This section should be expanded in future editions to incorporate material on the physiology of cardiovascular and pulmonary rehabilitation.

Chapter 15 details the body's adaptation to both acute and chronic high altitude exposure. Although Des Jardins states that an understanding of high altitude adaptation could aid in understanding the chronic hypoxia that characterizes pulmonary disease, he does not make the connection in this chapter. The material is interesting and well-presented, however. The effects of high pressure environments are well presented in Chapter 16. Although of primarily academic interest to most therapists, a number of key physiologic principles (eg, gas laws) are richly illustrated by this material. The book ends with a number of useful appendixes (units, symbols, and derivations of specific formulas).

This book is exceptional, both as a text and as a reference. It deserves to be on the bookshelf of every respiratory physiologist, physiology instructor, respiratory care instructor, and respiratory care student. Not only does it deserve to be on the bookshelf, but more importantly, it deserves to be pulled off the shelf and used often!

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Equipment Theory for Respiratory Care, 3rd edition. Gary C White MEd RRT CPFT. Albany: Delmar Publishers. 1999. Hardcover, illustrated, 674 pages, $66.95.

Equipment Theory for Respiratory Care, 3rd edition, uses a competency-based approach to the principles of respiratory equipment. The physical and operational principles of respiratory equipment and practice are inconsistently covered throughout each chapter in this textbook. However, the author does admit to a very simplistic approach to equipment theory and practice in his preface. This approach also admittedly incorporates a reading level below that of other texts in this category. Each chapter begins with a set of objectives that establishes what will be covered. Topic headings are bolded and facilitate finding the topic of interest. Basic equipment schematics and photographs accompany the text in each chapter. Rudimentary assembly and troubleshooting guides are provided for general equipment categories, as well as for a few manufacturers' specific devices. The author is commended for his attempt at incorporating troubleshooting algorithms. This is a unique and valuable approach. However, many of the algorithms are cumbersome and contain text and flow diagram errors.

"Clinical Corner" sections at the ends of the chapters present clinical scenarios and pose dilemmas that may occur in practice. The aim appears to be facilitation of classroom discussion on particular subject matter. Often the clinical scenarios pose questions that were not covered or were poorly covered in the text. However, the author offers no solutions or possible responses.

Clinical practice guidelines are not addressed in this textbook. The incorporation of practice guidelines would be a valuable addition. Although it is imperative for practitioners to understand how respiratory equipment works, it is equally if not more important to understand the guidelines for use in the clinical setting.

A multiple-choice self-assessment quiz is also offered at the conclusion of each chapter. As with the "Clinical Corner" sections, an answer key is not provided for the reader. The author suggests a minimum passing score on the self-assessment quiz for only a few of the chapters in the book.

A selected bibliography is provided at the conclusion of each chapter. No references are cited in the body of the text, making it difficult to verify what was written. The bibliography mainly references other books or manufacturers' operation manuals. Many of the references are 10 to 20 years old. There is minimal review of published peer-reviewed literature.

Chapter 1 addresses "Oxygen and Mixed Gas Therapy Equipment." This chapter discusses gas delivery theory, as well as the principles of operation for medical gas supply and monitoring equipment. Calculation examples, which accompany the formulas for the gas laws, are appropriate for entry level students. Some specific oxygen delivery devices are highlighted. The main focus of this chapter evolves around oxygen delivery. Only briefly does the author mention helium/oxygen and carbon dioxide/oxygen therapy.

Humidification and aerosol therapy equipment are discussed in Chapter 2. The author provides a brief overview of the fundamentals of humidification and aerosol therapy. The author is inconsistent in the

level of detail provided about humidification and aerosol equipment devices. The section on heat and moisture exchangers is glossed over. Similarly, the author briefly addresses the section dedicated to aerosol equipment. This chapter fails to differentiate between spacers and holding chambers. Illustrations accompanying printed instructions for metered-dose inhaler use would be a helpful addition.

Chapter 3, "Hyperinflation Therapy Equipment," heavily emphasizes intermittent positive-pressure breathing therapy, but the author acknowledges that use of this therapy has declined. Once again the author glosses over the rationale for use and principles of operation for all other forms of hyperinflation therapy described in this chapter. Clinical application is not blended in with equipment description and operation. The "Clinical Corner" section in this chapter poses questions that would be difficult to answer, since the chapter content does not address the issues raised. Patient monitoring considerations, hazards, and contraindications for equipment use were eliminated from this chapter.

Chapter 4 covers "Emergency Resuscitation Equipment." The layout of this chapter is fragmented and difficult to follow. Instructions for airway insertion and use are given without regard to whether the patient is an adult or child. Numerous errors on the correct procedure for insertion are noted. Although the author mentions in the chapter's introduction that not all artificial airways are indicated for emergency use, the particular airways are not identified. Additionally, this chapter does not consistently address sizing considerations, hazards, or contraindications for use. The author makes frequent references to the superior qualities suction equipment designs exhibit. This is evident in the discussion of the various types of suction catheters available for use. There is no scientific evidence cited to support the author's claim. This casts suspicion that the depth of knowledge the author has on the subject matter does not exceed what can be read in the product insert.

Adequate attention to detail in Chapter 5, "Physiologic Measurement and Monitoring Devices," is given. The questions in the chapter quiz are adequately covered in the text, and the clinical scenarios are relevant.

Chapter 6, "Mechanical Ventilator Theory and Practice," is well organized and well written. The author accurately describes the ventilator classification system developed by Robert Chatburn and recognizes his outstanding contributions to the theory of operation of mechanical ventilation. The questions in the chapter quiz are adequately covered in the text, and the clinical scenarios are relevant.

Chapter 7, "Adult Acute Care Ventilators: Ventilators Having Volume As a Control Variable," and Chapter 8, "Adult Acute Care Ventilators: Ventilators Having Flow and Pressure Control Variables," describe adult critical care ventilators in an organized and consistent manner. Many schematic diagrams are detailed, and ventilator photos provided. Chapter 9, "Pediatric and Neonatal Ventilators," presents pediatric and neonatal ventilators following the same format. Table 9–16 would be more useful if ventilator settings were listed. This would enable the reader to quickly compare ventilator options.

Chapter 10 describes home care and transport ventilators in a logical and organized manner, and the self-assessment questions are relevant and adequately covered in the text.

The final chapter, "High Frequency Mechanical Ventilation," describes the theory and operation of high-frequency mechanical ventilation. Graphical tracings complement the text. The "Clinical Corner" in this chapter is devoted to ventilator description and operation, rather than actually presenting clinical scenarios.

The author succeeded in providing a very simplistic approach to equipment theory. Despite the problems I have mentioned here, some chapters within the book merit the attention of respiratory therapy students and entry level practitioners.

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Treatment of the Hospitalized Cystic Fibrosis Patient. David M Orenstein and Robert C Stern, editors. (Lung Biology in Health and Disease, Volume 109, Claude Lenfant, Executive Editor.) New York: Marcel Dekker. 1998. Hardcover, illustrated, 446 pages, $180.

The numbers are convincing. Thirty thousand patients with cystic fibrosis (CF) in the United States, 30% of them hospitalized 1–3 times each year for a mean hospitalization of 11 days. It is with those figures in mind that the editors of **Treatment of the Hospitalized Cystic Fibrosis Patient** organized this comprehensive and well researched book. The mean life expectancy for a CF patient is now 32 years, and increasing steadily. Improvement in care, even in the absence of a cure, is directly responsible for this increase. The consequence of improved care is that the prevalence of hospitalized CF patients will continue to increase. More and more medical personnel are going to come in contact with CF patients. It is with the ideal of improving the care and the life of frequently hospitalized CF patients that the editors conceived this book.

Drs Stern and Orenstein, the editors, skillfully assembled individually written chapters into one cohesive volume. The topics span the spectrum of CF-related disease, from the initial diagnosis of CF to terminal care of the dying CF patient, and from surgical treatment of acute intestinal blockage to medical care of chronic pulmonary infection. Each chapter explores a particular issue in depth, such as "Nutrition and Electrolytes" and "Thoracic Surgery for Patients with Cystic Fibrosis," and there is little if any redundancy. Many of the chapters are so thorough that much of the book's content would be useful for general care of the CF patient rather than specific to the hospitalized patient.

Each chapter is well outlined in the table of contents, and the layout of the chapters is consistent. Each chapter contains numerous well reproduced illustrations, often radiographs or pathology slides, and helpful figures and charts. References are extensive and included at the end of each chapter. More importantly, the references are up to date. There is an extensive index, although the table of contents and its chapter outlines are more useful for focusing on specific topics.

The book is intended as a reference for physicians who care for CF patients, but would be valuable for respiratory therapists, nurses, medical students and trainees, pharmacists, and physician specialists who see CF patients only occasionally (eg, adult general surgeons). Each chapter provides both general principles and specific management guidelines that will be useful to any medical personnel who come in contact with a hospitalized CF patient. The book is well written in nontechnical language that is accessible to all medical personnel.

One of the more unusual aspects of the book is that, without detracting from its scholarly tone, it incorporates the individual

experiences of the authors. Care of CF patients is quickly changing. The authors' (most of whom have cared for CF patients for many years) experience speaks as much to the art of caring for the hospitalized patient as to the current science of caring for them. These physicians' experience is more apparent in some chapters than in others. For instance, the editors included a disclaimer that "no one will agree" with the whole chapter for the chapters "General Care of the Hospitalized Cystic Fibrosis Patient" and "Inpatient Treatment of Cystic Fibrosis Pulmonary Disease," both written by Dr Stern.

The editors were right. I did not agree with all their statements, but I did appreciate their perspective. Some of the more controversial statements regarded patients who "make a career" out of being hospitalized. I believe this is true of a subset of any group of patients with chronic disease, and the material may have been handled more delicately by dedicating a chapter to issues of chronic disease or growing up ill rather than embedded in a chapter on care of CF patients. In contrast, the chapter on "Terminal Care" was handled beautifully, weaving generalizations about terminal care with the specifics of terminal respiratory disease and prolonged illnesses.

The book is biased toward the pediatric CF patient, although there is a chapter entitled "Special Considerations for the Hospitalized Adult." This reflects the current state of clinical and research experience in CF, and I do not feel it detracts from the value of the book. In fact, as an adult pulmonologist, I found the chapters on early diagnosis and gastrointestinal disease particularly informative.

Treatment of the Hospitalized Cystic Fibrosis Patient is a successful addition to the Lung Biology in Health and Disease series. The editors fulfilled their mission and created an easy-to-read, clinically useful, and comprehensive volume that is a worthwhile read for any medical professional who comes in contact with a CF patient.

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Thoracic Imaging: A Practical Approach. Richard M Slone MD, Fernando R Gutierrez MD, Andrew J Fisher MD, with contributions from Matthew J Fleishman MD and Robert Y Kanterman MD. New York: McGraw-Hill. 1999. Hardcover, illustrated, 367 pages, $89.

Diseases of the chest involve a wide range of pathologies, affect a large number of patients, and are treated by a wide range of health care providers. As a result, books addressing pulmonary diseases must cover large amounts of material pertaining to diagnostic imaging techniques, differential diagnosis, and specifics about each disease, such as management, treatment, and prognosis. **Thoracic Imaging: A Practical Approach** is a concise yet thorough review of thoracic radiology, discussing the advantages and disadvantages of various diagnostic techniques, differential diagnosis, and specific diseases involving the chest.

The three authors, Drs Slone, Gutierrez, and Fisher, are recognized experts in the field of radiology, and have formulated a text that is full of pertinent information and marvelous case material. There are a total of 14 chapters and an appendix.

The first chapter is suited for all physicians and technicians or therapists caring for patients with thoracic diseases. This chapter is an overview of pulmonary anatomy and physiology, as well as discussing the arsenal of radiology examinations and blood gas analysis, pulmonary function testing, bronchoscopy, and mediastinoscopy.

Chapter 2 is a comprehensive listing of differential diagnoses based on radiographic and computed tomography appearance.

The next several chapters discuss specific lung diseases and mediastinal and cardiac pathology in a well organized approach. For example, there is a chapter discussing focal lung disease, such as pulmonary malignancy, and one discussing diffuse lung disease, such as acute respiratory distress syndrome. The mediastinum is well covered in this book, including diseases of the esophagus and the trachea.

There is an excellent chapter on cardiovascular diseases, including congenital cardiac disease. There are two chapters discussing abnormalities of the pleura, chest wall, and diaphragm. The chapter on congenital pulmonary disease and pediatrics, so often neglected in thoracic imaging texts, is a welcome inclusion. The presence of chapters on chest trauma and thoracic implants and devices speaks to the completeness of this textbook.

Chapter 11, the postsurgical and posttreatment chest, is outstanding, discussing the many new surgical techniques and procedures available, and their radiographic appearance.

A unique feature of this book is in Chapter 13, the discussion of the importance of evaluating the upper abdomen on conventional chest radiographs and on the inferior images from chest computed tomograms.

The last chapter discusses interventional radiology of the chest, and is an important chapter, not only for the radiologist performing the procedures, but also for the physician considering ordering these procedures.

The appendix serves as a reference for normal laboratory values, normal measurement of thoracic structures, cancer staging, and much more.

The book is intended for all radiologists, internists, and surgeons involved in the care of patients with chest disease. I believe this to be an excellent book for radiology residents, as well as pulmonary fellows in training. Its usefulness to respiratory therapists and technicians may be limited to a few chapters, but its well-written, concise format makes for easy reading.

The authors have succeeded in creating a handy, affordable reference book that complements the more expensive and comprehensive textbooks that cover thoracic radiology. As was the authors' intention, this is a "concise, yet complete, overview of thoracic imaging." The book is well organized, accurate, and written in a clear and concise manner. There are no wasted words.

The book is thoroughly referenced with current and state-of-the-art articles. The illustrations are expertly reproduced in the book, with the appropriate number of illustrations that enhance the text. The book is well indexed and the table of contents is extremely detailed.

I would highly recommend this book to all medical school libraries, radiology department libraries, and medical subspecialty libraries. I would also recommend this book as required reading for radiology residents. It will also serve as a nice review for radiologists in practice looking to improve their thoracic imaging knowledge.

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Ventilator Filter. Emergency Filtration Products introduces the RespAide Vapor Isolation Valve (VIV). According to the company, the device is a modularly designed filtration valve created for use with ISA compliant patient ventilation devices such as CPR masks, resuscitation bags, and endotracheal tubes. Emergency Filtration Products says the VIV has been tested and verified by an independent laboratory to have bacterial and viral filtration efficiencies of greater than 99.9% at 0.027 microns, and they say the device has a "duckbill" valve that closes automatically when the patient exhales to prevent any back-flow of breath or clogging the system if a patient regurgitates. For more information from Emergency Filtration Products, circle number 194 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

Vital Signs Monitor. Protocol Systems Inc has recently introduced the Propaq CS Vital Signs monitor. According to the company, the new portable monitor provides larger, more functional color display capabilities and is designed to meet more comprehensive bedside monitoring requirements. Protocol Systems says that the monitor provides a color, Thin Film Transfer, liquid crystal display measuring 8.4 inches diagonally and that it offers VGA resolution (640 horizontal x 480 vertical pixels) and pressure resistive dedicated touch zones. Company press materials state that the monitor can display up to four vital sign waveforms simultaneously including two vectors of electrocardiography. For more information from Protocol Systems Inc, circle number 195 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

Mask Seals. Hans Rudolph Inc has introduced two new mask seals they say improve comfort and seal integrity for users of Hans Rudolph's Nasal CPAP or full face mask. The company describes the Comfort Seal Foam as a disposable foam interface accessory for their nasal CPAP and full face masks designed to improve mask sealing and comfort for patients during CPAP and ventilation therapy or pulmonary function testing. Press materials say the foam seals are easy to apply and have a pressure-sensitive adhesive on one side that attaches to the mask. The company says the Ultimate Seal Gel is manufactured of a unique hydrogel material that is then molded in the geometry of the sealing surface of the Hans Rudolph nasal CPAP and full face masks. The company describes this gel seal as an optional accessory that allows greater comfort and the assurance of a leak-free fit. According to Hans Rudolph, the gel seal allows the skin to breathe while creating a comfortable barrier between the patient's skin and the mask. For more information from Hans Rudolph Inc, circle number 196 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

Oximetry Module. Mallinckrodt introduces the Nellcor® MP404 Oximetry Module. According to Mallinckrodt, the system provides customers advanced digital signal processing designed to track patient oxygen status even during long periods of patients' motion or of poor perfusion. Company press materials also reveal that upgraded algorithms allow the MP404 to read through signal corruption to provide accurate patient saturation and pulse values. For more information from Mallinckrodt, circle number 197 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

www.rcjournal.com

Not-for-profit organizations are offered a free advertisement of up to eight lines to appear, on a space-available basis, in Calendar of Events in RESPIRATORY CARE. Ads for other meetings are priced at $5.50 per line and require an insertion order. Deadline is the 20th of the month two months preceding the month in which you wish the ad to run. Submit copy and insertion orders to Calendar of Events, RESPIRATORY CARE, 11030 Ables Lane, Dallas TX 75229-4593.

Calendar of Events

AARC & AFFILIATES

June 10, 17, 24–*Alabama*

The ASRC is sponsoring three educational conferences: June 10 in Tuscaloosa with 3 CEU credits from the AARC, June 17 in Cullman (Huntsville) with 4 CEUs, and June 24 in Montgomery with 3 CEUs. Topics include NIPPV, acute MI, mechanically ventilated patients, minimally invasive thoracic surgery, and stress management. **Contact:** The ASRC at (334) 434-3405 or **http://asrc.fsn.net**.

June 14-16—*Round Top, New York*

The New Jersey and New York State Societies for Respiratory Care host their 13th annual Spring Forum (formerly known as the Managers/Educators "Rocking Chair" Conference) at the Riedlbauer Resort. Speakers include AARC President Garry Kauffman, Clatie Campbell, Ralph Cavallo, Ken Wyka, Joe Sorbello, John Rutkowski, Sandy McCleaster, and George Gaebler. Topics will cover time management, team building, reducing apathy, and instilling motivation. Nine CRCE units have been requested. It is open to all RCPs but should be of special interest to supervisors, managers, educators, and those practicing in alternate sites. **Contact:** Ken Wyka at (201) 288-3959 or Joe Sorbello at (315) 464-6872.

July 17–18–*Reno, Nevada*

The NSRC will host their annual state conference and exhibit at the Silver Legacy Resort Casino by Lake Tahoe. Ten CEUs are pending. **Contact:** Call John Steinmetz at (775) 348-5537.

September 14–15–*Pittsburgh, Pennsylvania*

The PSRC Western Regional Pulmonary Conference will be held in conjunction with The Greater Pittsburgh Sleep Professionals at the Sheraton Station Square. The conference features education presentations on management, critical care, sleep diagnostics, pulmonary rehabilitation, the physician forum, and the GPSP sleep tract. **Contact:** Debbie Logan at (800) 545-4663, ext. 112.

September 20-22—*Rochester, Minnesota*

The Minnesota Society for Respiratory Care host their 31st Annual Fall State Conference — "Too Hot to Handle." **Contact:** For more information, contact Laurie Tomaszewski at (651) 232-1922, Carolyn Dunow at **dunowc@fhpcare.com**, or Carl Mottram at **mottram.carl@mayo.edu**.

October 11–13–*Bossier City, Louisiana*

The LSRC's second annual Fall Convention will be held at the Isle of Capri Hotel and Casino with numerous national speakers and exhibitors. Ten CEUs will be available. **Contact:** For more information or booth reservations, call Shonda Houston at (318) 226-0555 or e-mail **sparta@lsumc.edu**.

Other Meetings

June 15-16—*Cheyenne, Wyoming*

United Medical Center will hold its Annual Critical Care Seminar at the Terry Bison Ranch just eight miles south of Cheyenne on the Wyoming and Colorado border. Topics include hemodynamic monitoring, balloon pump troubleshooting, acute MI, status asthma, acute head injury and neuromuscular crisis in the adult and pediatric patient, RSV in the newborn and children, and variances in care and monitoring of the ventilator patient. Ten CEUs have been requested from the AARC. **Contact:** Contact Steve McPherson at (307) 633-7700 or **SMc@UMCWY.org**.

June 8–11–*Chicago, Illinois*

The American Academy of Pediatrics' Transport Section is hosting two conferences in one. The 2000 Conference on Neonatal/Pediatric Critical Care Transport is scheduled June 8–10 at the Hotel Inter-Continental. Following it on June 10–11 at the same location is Leadership: Evolution, Current Status, and Planning for the Future. CRCE credits have been requested. **Contact:** For more information, call (800) 433-9016 or log on to **www.aap.org**.

July 29–30–*Chicago, Illinois*

The Association of Asthma Educators (AAE) is sponsoring Conference 2000 at the Chicago Marriott O'Hare. The conference is geared toward allied health professionals involved and/or interested in asthma education. Topics will include new medication and devices, educational issues addressing diverse practice settings as well as special populations, and issues in asthma educator certification. Continuing education is offered for nurses, RTs, pharmacists, and Category 1 CME for physicians, nurse practitioners, and physician assistants. **Contact:** The AAE at (888) 988-7747 or e-mail **berrihm@swbell.net**.

August 13-18—*Hobertus, Wisconsin*

The American Lung Association of Metropolitan Chicago is looking for a volunteer RT with a special interest in respiratory care for children. The RT will volunteer their time and provide structured asthma education one hour a day to children at the 18th annual CampACTION at YMCA Camp Minikani. The RT will also provide individual education in the cabins. Up to eight CEU credits are available. CampACTION is staffed 24 hours a day by physicians, nurses, an RT, and a pharmacist. **Contact:** If interested, call Evet Hexamer at (312) 243-2000, ext. 260.

August 18–19–*Tampa, Florida*

The Alliance for Cardiovascular Professionals (ACP) and TechEd Consultants are sponsoring a spirometry course at the Saddlebrook Resort in conjunction with the ACP annual meeting. Tuition will be discounted for ACP and FSRC members. **Contact:** Call ACP at (540) 370-0102 or TechEd at (517) 676-7018.

Practical Spirometry Certification Course

Two-day hands-on NIOSH-approved course presented by Mayo Pulmonary Services: Sept. 29–30 in Chicago, IL; and Nov. 9–10 in Rochester, MN. NIOSH approval #57. Approved by AAOHN for 15.6 contact hours. **Contact:** For further details, call (800) 533-1653.

American Association for Respiratory Care

MEMBERSHIP APPLICATION

Please read the eligibility requirements for each of the classifications in the right-hand column, then complete the applicable section. All information requested below must be provided, except where indicated as optional. See other side for more information and fee schedule. Please sign and date application on reverse side and type or print clearly. Processing of application takes approximately 15 days.

- ☐ Active
- Associate
  - ☐ Foreign
  - ☐ Physician
  - ☐ Industrial
- ☐ Special
- ☐ Student

Last Name _____

First Name _____

Social Security No. _____

Home Address _____

City _____

State _____ Zip __ __ __ __ __ — __ __ __ __

Phone No. (_____) _____

Primary Job Responsibility (check one only)

- ☐ Technical Director
- ☐ Assistant Technical Director
- ☐ Pulmonary Function Specialist
- ☐ Instructor/Educator
- ☐ Supervisor
- ☐ Staff Therapist
- ☐ Staff Technician
- ☐ Rehabilitation/Home Care
- ☐ Medical Director
- ☐ Sales
- ☐ Student
- ☐ Other, specify _____

Type of Business

- ☐ Hospital
- ☐ Skilled Nursing Facility
- ☐ DME/HME
- ☐ Home Health Agency
- ☐ Educational Institution
- ☐ Manufacturer or supplier
- ☐ Other, specify _____

Date of Birth (optional) _____ Sex (optional) _____

U.S. Citizen? _____ Yes _____ No

Have you ever been a member of the AARC? _____

If so, when? From _____ to _____

Preferred mailing address: ☐ Home ☐ Business

For office use only

FOR ACTIVE MEMBER

An individual is eligible if he/she lives in the U.S. or its territories or was an Active Member prior to moving outside its borders or territories, and meets ONE of the following criteria: (1) is legally credentialed as a respiratary care professional if employed in a state that mandates such, OR (2) is a graduate of an accredited educational program in respiratory care, OR (3) holds a credential issued by the NBRC. An individual who is an AARC Active Member in good standing on December 8, 1994, will continue as such provided his/her membership remains in good standing.

PLEASE USE THE ADDRESS OF THE LOCATION WHERE YOU PERFORM YOUR JOB, NOT THE CORPORATE HEADQUARTERS IF IT IS LOCATED ELSEWHERE.

Place of Employment _____

Address _____

City _____

State _____ Zip __ __ __ __ __ - __ __ __ __

Phone No. (_____) _____

Medical Director/Medical Sponsor _____

FOR ASSOCIATE OR SPECIAL MEMBER

Individuals who hold a position related to respiratary care but do not meet the requirements of Active Member shall be Associate Members. They have all the rights and benefits of the Association except to hold office, vote, or serve as chair of a standing committee. The following subclasses of Associate Membership are available: Foreign, Physician, and Industrial (individuals whose primary occupation is directly or indirectly devoted to the manufacture, sale, or distribution of respiratory care equipment or supplies). Special Members are those not working in a respiratory care-related field.

PLEASE USE THE ADDRESS OF THE LOCATION WHERE YOU PERFORM YOUR JOB, NOT THE CORPORATE HEADQUARTERS IF IT IS LOCATED ELSEWHERE.

Place of Employment _____

Address _____

City _____

State _____ Zip __ __ __ __ __ - __ __ __ __

Phone No. (_____) _____

FOR STUDENT MEMBER

Individuals will be classified as Student Members if they meet all the requirements for Associate Membership and are enrolled in an educational program in respiratory care accredited by, or in the process of seeking accreditation from, an AARC-recognized agency.

SPECIAL NOTICE — Student Members do not receive Continuing Respiratory Care Education (CRCE) transcripts. Upon completion of your respiratary care education, continuing education credits may be pursued upon your reclassification to Active or Associate Member.

School/RC Program _____

Address _____

City _____

State _____ Zip __ __ __ __ __ - __ __ __ __

Phone No. (_____) _____

Length of program

- ☐ 1 year
- ☐ 2 years
- ☐ 4 years
- ☐ Other, specify _____

Expected Date of Graduation *(REQUIRED INFORMATION)*

Month _____ Year _____

American Association for Respiratory Care • 11030 Ables Lane • Dallas, TX 75229-4593 • [972] 243-2272 • Fax [972] 484-2720

American Association for Respiratory Care **MEMBERSHIP APPLICATION**

Demographic Questions

We request that you answer these questions in order to help us design services and programs to meet your needs.

Check the Highest Degree Earned

- ☐ High School
- ☐ RC Graduate Technician
- ☐ Associate Degree
- ☐ Bachelor's Degree
- ☐ Master's Degree
- ☐ Doctorate Degree

Number of Years in Respiratory Care

- ☐ 0-2 years
- ☐ 3-5 years
- ☐ 6-10 years
- ☐ 11-15 Years
- ☐ 16 years or more

Job Status

- ☐ Full Time
- ☐ Part Time

Credentials

- ☐ RRT
- ☐ CRT
- ☐ Physician
- ☐ CRNA
- ☐ RN
- ☐ LVN/LPN
- ☐ CPFT
- ☐ RPFT
- ☐ Perinatal/Pediatric

Salary

- ☐ Less than $10,000
- ☐ $10,001-$20,000
- ☐ $20,001-$30,000
- ☐ $30,001-$40,000
- ☐ $40,000 or more

PLEASE SIGN

I hereby apply for membership in the American Association for Respiratory Care and have enclosed my dues. If approved for membership in the AARC, I will abide by its bylaws and professional code of ethics. I authorize investigation of all statements contained herein and understand that misrepresentations or omissions of facts called for is cause for rejection or expulsion.

A yearly subscription to RESPIRATORY CARE journal and *AARC Times* magazine includes an allocation of $11.50 from my dues for each of these publications.

NOTE: Contributions or gifts to the AARC are not tax deductible as charitable contributions for income tax purposes. However, they may be tax deductible as ordinary and necessary business expenses subject to restrictions imposed as a result of association lobbying activities. The AARC estimates that the nondeductible portion of your dues — the portion which is allocable to lobbying — is 26%.

Signature _____

Date _____

Membership Fees

Payment must accompany your application to the AARC. Fees are for 12 months. (NOTE: Renewal fees are $75.00 Active, Associate-Industrial or Associate-Physician, or Special status; $90.00 for Associate-Foreign status; and $45.00 for Student status).

☐ Active	$ 87.50
☐ Associate (Industrial or Physician)	$ 87.50
☐ Associate (Foreign)	$102.50
☐ Special	$ 87.50
☐ Student	$ 45.00
TOTAL	$_____

Specialty Sections

Established to recognize the specialty areas of respiratary care, these sections publish a bi-monthly newsletter that focuses on issues of specific concern to that specialty. The sections also design the specialty programming at the national AARC meetings.

☐ Adult Acute Care Section	$15.00
☐ Education Section	$20.00
☐ Perinatal-Pediatric Section	$15.00
☐ Diagnostics Section	$15.00
☐ Continuing Care-Rehabilitation Section	$15.00
☐ Management Section	$20.00
☐ Transport Section	$15.00
☐ Home Care Section	$15.00
☐ Subacute Care Section	$15.00
TOTAL	$_____

GRAND TOTAL = Membership Fee plus optional sections $_____

- ☐ Total Amount Enclosed/Charged $_____
- ☐ Please charge my dues (see below)

To charge your dues, complete the following:

- ☐ MasterCard
- ☐ Visa

Card Number

— — — — — — — — — — — — — — — —

Card Expires _____/_____

Signature _____

Mail application and appropriate fees to:

American Association for Respiratory Care • 11030 Ables Lane • Dallas, TX 75229-4593 • (972) 243-2272 • Fax (972) 484-2720

Manuscript Preparation Guide

RESPIRATORY CARE welcomes original manuscripts related to the science and technology of respiratory care and prepared according to the following instructions and the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* (available at http://www.acponline.org/journals/resource/unifreqr.htm). Manuscripts are blinded and reviewed by professionals who are experts in their fields. Authors are responsible for obtaining written permission to publish previously–published figures and tables from the original copyright holder. Accepted manuscripts are copyedited for clarity, concision, and consistency with RESPIRATORY CARE format. Before publication, authors receive page proofs for minor correction. Published papers are copyrighted by Daedalus Inc and may not be published elsewhere without permission. Editorial consultation is available at any stage of planning or writing for any submission; contact the Editorial Office.

Categories of Articles

Research Article: A report of an original investigation (a study). Must include Title Page, Abstract, Key Words, Background, Methods, Results, Discussion, Conclusions, and References. May also include Tables, Figures (if so, must include Figure Legends), Acknowledgments, and Appendices.

Review Article: A comprehensive, critical review of the literature and state-of-the-art summary of a topic that has been the subject of at least 40 published research articles. Must include: Title Page, Outline, Key Words, Introduction, Review of the Literature, Summary, and References. May also include: Tables, Figures (if so, must include Figure Legends), and Acknowledgments.

Overview: A critical review of a pertinent topic that has fewer than 40 published research articles. Same structure as Review Article.

Update: A report of subsequent developments in a topic that has been critically reviewed in RESPIRATORY CARE or elsewhere. Same structure as a Review Article.

Special Article: A pertinent paper not fitting one of the other categories. Consult with the Editor before writing or submitting such a paper.

Editorial: A paper addressing an issue in the practice or administration of respiratory care. It may present an opposing opinion, clarify a position, or bring a problem into focus.

Letter: A brief, signed communication responding to an item published in RESPIRATORY CARE or about other pertinent topics. Tables, Figures, and References may be included. The letter should be marked "For Publication."

Case Report: Report of an uncommon clinical case or a new or improved method of management or treatment. A case-managing physician must either be an author or furnish a letter approving the manuscript. Must include: Title Page, Abstract, Introduction, Case Summary, Discussion, and References. May also include: Tables, Figures (if so, must include Figure Legends), and Acknowledgments.

Point-of-View Paper: A paper expressing personal but substantiated opinions on a pertinent topic. Must include: Title Page, Text, and References. May also include Tables and Figures (if so, must include Figure Legends).

Drug Capsule: A miniature review paper about a drug or class of drugs that includes discussions of pharmacology, pharmacokinetics, or pharmacotherapy.

Graphics Corner: A brief case report discussing and illustrating waveforms for monitoring or diagnosis. Should include Questions, Answers, and Discussion sections.

Kittredge's Corner: A brief description of the operation of respiratory care equipment. Should include information from manufacturers and editorial comments and suggestions.

PFT Corner: A brief, instructive case report including pulmonary function testing, accompanied by a review of the relevant physiology and appropriate references to the literature.

Test Your Radiologic Skill: A brief, instructive case report involving pulmonary medicine radiography and including one or more radiographs. May involve imaging techniques other than conventional chest radiography.

Review of a Book, Film, Tape, or Software: A balanced, critical review of a recent release. RESPIRATORY CARE does not accept unsolicited book reviews; please contact the Editor if you have a suggestion for a book review.

Preparing the Manuscript

Print on one side of white 8.5 ×11 inch paper, with margins of at least 1 inch on all sides. Double-space the text and number the pages. Do *not* include author names, author institutional affiliations, or allusions to institutional affiliations anywhere except on the title page. On the Abstract page include the title but do not include author names. Begin each of the following on a new page: Title Page, Abstract, Text, Acknowledgments, References, each Table, each Figure, and each Appendix. Use standard English in the first person and active voice. Type all headings in initial-capital letters (eg, Background, Methods, Patients, Equipment, Statistical Analysis, Results, Discussion). Center the main section headings and place second-level headings on the left margin.

Abstract. Please ensure that the abstract does not contain any facts or conclusions that do not also appear in the body text. Limit the abstract to no more than 400 words.

Key Words. Research, Review, Overview, and Special Articles require Key Words. On the Abstract or Outline page, include a list of 6 to 10 key words or two-word phrases.

References. Assign reference numbers in the order that articles are cited in your manuscript. At the end of your manuscript, list the cited works in numerical order. Abbreviate journal names as in *Index Medicus*. List all authors. The following examples show RESPIRATORY CARE's style for references.

Article in a journal carrying pagination throughout the volume:

> Rau JL, Harwood RJ. Comparison of nebulizer delivery methods through a neonatal endotracheal tube: a bench study. Respir Care 1992;37(11):1233-1240.

Article in a publication that numbers each issue beginning with Page 1:

> Bunch D. Establishing a national database for home care. AARC Times 1991;15(Mar):61,62,64.

Corporate author journal article:

> American Association for Respiratory Care. Criteria for establishing units for chronic ventilator-dependent patients in hospitals. Respir Care 1988;33(11):1044-1046.

Article in journal supplement: (Journals differ in numbering and identifying supplements. Supply information sufficient to allow retrieval.)

> Reynolds HY. Idiopathic interstitial pulmonary fibrosis. Chest 1986; 89(3 Suppl):139S-143S.

Abstract in journal: (Abstracts citations are to be avoided, and those more than 3 years old should not be cited.)

> Stevens DP. Scavenging ribavirin from an oxygen hood to reduce environmental exposure (abstract). Respir Care 1990;35(11): 1087-1088.

Editorial in a journal:

> Enright P. Can we relax during spirometry? (editorial). Am Rev Respir Dis 1993;148(2):274.

Editorial with no author given:

> Negative-pressure ventilation for chronic obstructive pulmonary disease (editorial). Lancet 1992;340(8833):1440-1441.

Letter in journal:

> Aelony Y. Ethnic norms for pulmonary function tests (letter). Chest 1991;99(4):1051.

Corporate author book:

> American Medical Association Department of Drugs. AMA drug evaluations, 3rd ed. Littleton CO: Publishing Sciences Group; 1977.

Book: (For any book, specific pages should be cited whenever reference is made to specific statements or other content.)

> DeRemee RA. Clinical profiles of diffuse interstitial pulmonary disease. New York: Futura; 1990:76-85.

Chapter in book with editor(s):

> Pierce AK. Acute respiratory failure. In: Guenter CA, Welch MH, editors. Pulmonary medicine. Philadelphia: JB Lippincott; 1977:26-42.

Paper accepted but not yet published:

> Hess D. New therapies for asthma. Respir Care (year, in press).

Personal communication of unpublished data not yet accepted for publication: You must obtain written permission to cite unpublished data received via personal communication. Do not number such references, but instead make parenthetical reference in the body text of your manuscript. Example: "Recently, Jones found this treatment effective in 45 of 83 patients (Jones HI, University of the Cascades, 1999, personal communication)."

Tables. Tables should be consecutively numbered. Start each table on a separate page. Number and title the table and give each column a brief heading. Place explanations in footnotes, including all nonstandard abbreviations and symbols. Key the footnotes with the following symbols, superscripted, in the table body, and in the following order: *, †, ‡, §, ‖, ¶, **, ††. Do not use horizontal or vertical rules or borders. Do not submit tables as photographs, reduced in size, or on oversize paper.

Figures (illustrations). Figures include graphs, line drawings, photographs, and radiographs. Use only illustrations that clarify and augment the text. Number figures consecutively as Figure 1, Figure 2, etc. All the figures must be mentioned in the text. Every figure should have a legend (a title and/or description explaining the figure). Figure legends should appear as separate paragraphs at the end of the manuscript (after the References section), in the same computer file as the manuscript (not in a separate file, as with the tables and figures). Do not create scanned versions of figures borrowed from other publications; clear photocopies are preferable. To include figures previously published in other publications, you must obtain permission from the original copyright holder (see below). Figures must be of professional quality and a copy of the article from which the figure came should be available. If color is essential to the figure, consult the Editor for more information. In reports of animal experiments, use schematic drawings, not photographs. A letter of consent must accompany any photograph of an identifiable person. If possible, submit radiographs as prints and full-size copies of film.

Drugs. Precisely identify all drugs and chemicals used, giving generic names, doses, and methods of administration. Brand names may be given in parentheses after generic names.

Commercial Products. In the text, parenthetically identify commercial products only on first mention, giving the manufacturer's name, city, and state or country. Example: "We performed spirom-

etry (1085 System, Medical Graphics, Minneapolis, Minnesota)." Provide model numbers if available, and manufacturer's suggested price, if the study has cost implications.

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Ethics. When reporting experiments on human subjects, indicate that procedures were conducted in accordance with the ethical standards of the *World Medical Association Declaration of Helsinki* (see Respir Care 1997;42(6):635-636) or of the institution's committee on human experimentation. State that informed consent was obtained. Do not use patient's names, initials, or hospital numbers in text or illustrations. When reporting experiments on animals, indicate that the institution's policy, a national guideline, or a law on the care and use of laboratory animals was followed.

Statistics. Identify the statistical tests used in analyzing the data and give the prospectively determined level of significance in the Methods section. Report actual p values in the Results section. Cite only textbook and published article references to support choices of tests. As with commercial products (see above), parenthetically identify any general-use or commercial computer programs used.

Units of Measurement. Express measurements of length, height, weight, and volume in metric units appropriately abbreviated; temperatures in degrees Celsius; and blood pressures in millimeters of mercury (mm Hg). Report hematologic and clinical-chemistry measurements in conventional metric and in SI (*Système Internationale*) units (units and conversion factors listed at Respir Care 1997;42(6):640). Show gas pressures (including blood gas tensions) in millimeters of mercury (mm Hg).

Conflict of Interest. On the cover page, authors must disclose any liaison or financial arrangement they have with a manufacturer or distributor whose product is addressed in the manuscript or with the manufacturer or distributor of a competing product. Such arrangements do not disqualify a paper from consideration and are not disclosed to reviewers. Reviewers are screened for possible conflict of interest.

Abbreviations and Symbols. Use standard abbreviations and symbols, listed at Respir Care 1997;42(6):637-642. Do not create new abbreviations. Do not use abbreviations in the title, in section headings, and do not use unusual abbreviations in the abstract. Use an abbreviation only if the term occurs 4 or more times in the paper. Define all abbreviations (ie, write out the full term on first mention, followed by the abbreviation in parentheses) and thereafter use only the abbreviation. Standard units of measurement and scientific terms can be abbreviated without explanation (eg, L/min, mm Hg, pH, O_2). Please use the following forms: cm H_2O (not cmH_2O), f (not bpm), L (not l), L/min (not LPM, l/min, or lpm), mL (not ml), mm Hg (not mmHg), pH (not Ph or PH), $p > 0.001$ (not p>0.001), s (not sec), S_{pO_2} (arterial oxygen saturation measured via pulse-oximetry).

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Authorship. All persons listed as authors should have participated in the reported work and in the shaping of the manuscript, all must have proofread the submitted manuscript, and all should be able to publicly discuss and defend the paper's content. A paper of corporate authorship must specify the key persons responsible for the article. Attribution of authorship is not based solely on solicitation of funding, collection or analysis of data, provision of advice, or similar services. Persons who provide such ancillary services may be recognized in an Acknowledgments section.

Reviewers: Please supply the names, credentials, affiliations, addresses, and phone/fax numbers of 3 professionals whom you consider expert on the topic of your paper. Your manuscript may be sent to one or more of them for blind peer review.

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Submit three printed copies and one (3.5-inch) computer diskette. The printed copies should each include photocopies of all of the Figures, Tables, and Appendixes. On the diskette, the manuscript should be in one file and the tables in a separate file. If soft copies of the figures are available, they should also be in a separate file. *However, do not create scanned versions of figures borrowed from other publications; clear photocopies are preferable.* Include the completed Cover Letter and Checklist (see next page) and permission letters. Mail to RESPIRATORY CARE, 600 Ninth Avenue, Suite 702, Seattle WA 98104. Do not fax manuscripts. Receipt will be acknowledged.

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"We, the undersigned, have all participated in the work reported, proofread the accompanying manuscript, and approve its submission for publication." Please print and include credentials, title, institution, academic appointments, city and state. If more than 4 authors, please use another copy of this form.*

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*Second Author: _____

Author Signature/Date _____

*Third Author: _____

Author Signature/Date _____

*Fourth Author: _____

Author Signature/Date _____

Has this research been presented in any public forum? ❑ Yes ❑ No

If yes, where, when and by whom? _____

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- ❑ Have you enclosed a copy of the manuscript on diskette?
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MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Page ____ of ____

Form Approved: OMB No. 0910-0291 Expires: 4/30/96
See OMB statement on reverse

FDA Use Only (Resp Care)

Triage unit sequence #

A. Patient information

Patient Identifier	2. Age at time of event: or Date of birth:	3. Sex	4. Weight
In confidence		☐ female ☐ male	____ lbs or ____ kgs

B. Adverse event or product problem

☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

Outcomes attributed to adverse event (check all that apply)

- ☐ death ____ (mo/day/yr)
- ☐ life-threatening
- ☐ hospitalization – initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other: ____

3. Date of event (mo/day/yr)	4. Date of this report (mo/day/yr)

Describe event or problem

Relevant tests/laboratory data, including dates

Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   #1
   #2

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1	#1
#2	#2

4. Diagnosis for use (indication)
   #1
   #2

5. Event abated after use stopped or dose reduced
   #1 ☐ yes ☐ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)	7. Exp. date (if known)
#1	#1
#2	#2

8. Event reappeared after reintroduction
   #1 ☐ yes ☐ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # (for product problems only)
   – –

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device
   - ☐ health professional
   - ☐ lay user/patient
   - ☐ other: ____
5. Expiration date (mo/day/yr)
6. model # ____
   catalog # ____
   serial # ____
   lot # ____
   other # ____
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
   ☐ yes ☐ no ☐ returned to manufacturer on ____ (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name & address	phone #

2. Health professional?	3. Occupation	4. Also reported to
☐ yes ☐ no		☐ manufacturer ☐ user facility ☐ distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

FDA

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or FAX to:
1-800-FDA-0178

(Form 3500 1/96)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ADVICE ABOUT VOLUNTARY REPORTING

Report experiences with:

- medications (drugs or biologics)
- medical devices (including in-vitro diagnostics)
- special nutritional products (dietary supplements, medical foods, infant formulas)
- other products regulated by FDA

Report SERIOUS adverse events. An event is serious when the patient outcome is:

- death
- life-threatening (real risk of dying)
- hospitalization (initial or prolonged)
- disability (significant, persistent or permanent)
- congenital anomaly
- required intervention to prevent permanent impairment or damage

Report even if:

- you're not certain the product caused the event
- you don't have all the details

Report product problems – quality, performance or safety concerns such as:

- suspected contamination
- questionable stability
- defective components
- poor packaging or labeling
- therapeutic failures

How to report:

- just fill in the sections that apply to your report
- use section C for all products except medical devices
- attach additional blank pages if needed
- use a separate form for each patient
- report either to FDA or the manufacturer (or both)

Important numbers:

- 1-800-FDA-0178 to FAX report
- 1-800-FDA-7737 to report by modem
- 1-800-FDA-1088 to report by phone or for more information
- 1-800-822-7967 for a VAERS form for vaccines

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

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Pediatric Ventilation: Kids Are Different—Mark Heulitt MD; Host, Richard Branson RRT—Video July 25; Audio August 15

What Matters in Respiratory Monitoring: What Goes and What Stays—Dean Hess PhD RRT FAARC; Host, Richard Branson RRT—Video August 22; Audio September 26

Managing Asthma: An Update—Patti Joyner RRT CCM; Host, Mari Jones MSN RN RRT—Video September 19; Audio October 17

Routine Pulmonary Function Testing: Doing It Right—Carl D Mottram RRT RPFT; Host, David Pierson MD—Video November 7; Audio December 5

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- American Respiratory Care Foundation fellowships, grants, & awards
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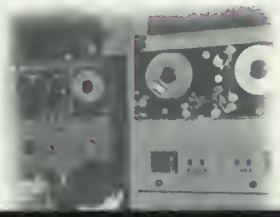

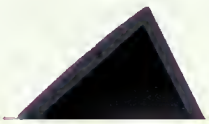

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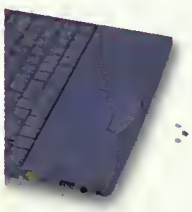

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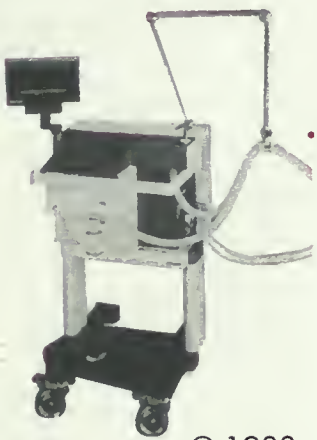

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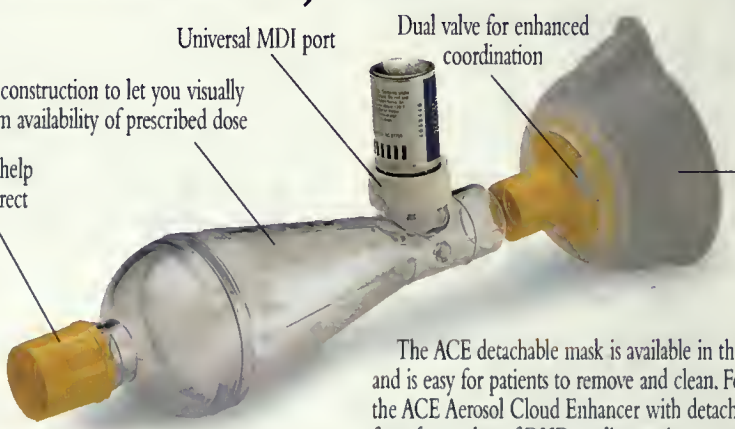
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